

REMARKS

Claims 1 – 8, 10 – 30, 34, 38 – 41, and 44 – 54 were pending in the instant application. Amendment of claims 1 and 52 – 54 is requested herein. New claims 55 – 61 are added, and no claims are cancelled. Upon entry of the amendment presented herein, claims 1 – 8, 10 – 30, 34, 38 – 41, and 44 – 61 will be pending.

Support for the claim amendments may be found throughout the specification and claims as originally filed. The new claims are directed to esters, amides, and prodrugs as disclosed, for example, in claim 1 as filed and at pp.44 – 45 of the application. No new matter has been added. The recitation of R⁷ has been stricken from claims 1 and 52 – 54. Also, chemical formula I in claims 1 and 52 – 53 has been replaced with the analogous chemical formula in claim 1 as filed. That is, the amendments to the claim concerning the alternative substitution of the indicated nitrogen atom with an “R⁷” group are withdrawn. The previous amendments relating to R⁷ were based on a mistaken understanding of the disclosure of the specification and therefore submitted erroneously. Accordingly, the characterization of the compounds 9b, 9e, 9y, and 9z, as well as 9a, 9q, 9r, 9s, 9cc, and 9ee in the Amendment and Response of July 30, 2002, should be disregarded. Likewise, the previous amendment to claim 1, in which the group -NH-SO₂-(C₁-C₆-alkyl) was added to the definition of “J,” was based on the same misunderstanding and is similarly withdrawn. The definition of J in each of claims 52 – 54 is also amended to remove the recitation of -NH-SO₂-(C₁-C₆-alkyl), and the previous remarks concerning the compound 3d should be disregarded. The previously submitted erroneous claim amendments are believed to be rectified by the present Amendment and Response.

Amendment of the claims herein should in no way be construed as an acquiescence to any of the rejections/objections set forth in the instant Office Action, or in any previous Office Action, and was done solely to expedite prosecution of the above-identified application. Applicants reserve the option to prosecute the same or similar claims as those originally filed in the instant application or one or more or subsequent applications.

Attached hereto as Appendix, captioned “*Version with markings to show changes made*”, is a marked-up version of the changes made to the claims by the amendments presented herein.

Attorney Docket Number

The attorney docket number for the present application, as captioned above, is **BBI-5037CPUSCPA**. A request for change in attorney docket number to BBI-5037CPUSCPA from 5500-01-TMC was submitted with the continued prosecution application on October 23, 2002. The cover page accompanying the present Office Action (form "PTO-90C") nevertheless refers to the prior docket number. The undersigned respectfully requests that the Office up-date its records to reflect this change in attorney docket number.

Claim Rejections - 35 U.S.C. §112

Rejection of Claims 1 – 8, 10 – 30, 52, and 53 under 35 U.S.C. §112, First Paragraph

The present Office Action rejects claims 1 – 8, 10 – 30, 52, and 53 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. In particular, the Office Action objects to the "new variable" R⁷. As noted above, the recitation of this variable in the claims has been deleted, and the claims have been further amended to conform with this deletion. Accordingly, this rejection is believed to be overcome and reconsideration thereof is requested.

Rejection of Claims 1 – 8, 10 – 30, and 54 under 35 U.S.C. §112, Second Paragraph

The Office Action also rejects claims 1 – 8, 10 – 30, and 54 under 35 U.S.C. §112, second paragraph, as being indefinite for the reasons described below. Although the Office Action specifically states that claims 1 – 8, 10 – 30, and 54 are rejected under this section of the patent statute, reasoned statements are only presented for the rejections of claims 1, 17, and 54.

In particular, the Office Action states that claim 1 has been amended to include, *inter alia*, a proviso excluding specific compounds, and that some of the compounds within the proviso contain a heterocyclic group. The Office Action also notes that the Remarks accompanying the amendment to claim 1 state that the claims have been "amended to delete any reference to heterocycle or heteroaryl, so that the claims no longer read on non-elected subject

matter.” The Office Action seek clarification if heterocyclic compounds are “meant to be included in formula I” of claim 1.

Applicants reiterate that the scope of claim 1, and indeed all of the claims, is intended to comply with the aforementioned restriction requirement (dated October 25, 1999, paper no. 4). Consequently, the recitation of certain compounds in the proviso of claim 1 is redundant. In order to clarify the scope of claim 1 and in the interest of furthering prosecution, the proviso of claim 1 has been amended herein to delete reference to compounds containing heterocyclic groups.

Additionally, the Office Action states that the list of compounds within the proviso of claim 1 includes an adamantyl compound, *i.e.*, a polycyclic compound. The Office Action then alleges, incorrectly, that “the definition of ‘cycloalkyl’ in the specification . . . is limited to monocyclic moieties.” The particular section of the specification (at page 40) that the Office Action refers to reads as follows:

The term “cycloalkyl” means a cyclic alkyl group. Examples of cycloalkyl groups include cyclopropane, cyclobutane, cyclopentane, and cyclohexane.

Although the definition of “cycloalkyl” certainly includes the four monocyclic groups exemplified in the quoted passage, there is nothing in the specification to indicate that the meaning of “cycloalkyl” should be limited to only monocyclic moieties as the Office Action alleges. To the contrary, the specification expressly indicates that **polycyclic** compounds are meant to be included. In this regard, consider **compound 4d** at page 82. This compound has an R¹ group containing a **bicyclo[2.2.1]heptane group**. Applicants therefore assert that one skilled in the art would have understood the term “cycloalkyl” as used in the specification to include monocycloalkyl, bicycloalkyl, polycycloalkyl groups, unless indicated otherwise. Therefore, regarding the word “cycloalkyl,” the claims are believed to comply with the requirements of section 112, and reconsideration of this rejection is requested.

The Office Action states that claim 17 is vague because it apparently further defines claim 1 by specifying particular groups for R¹ and R³, and the Office Action states that the

possibilities recited in the claim for these two moieties are inconsistent. Clarification of this rejection is requested. Claim 17 as amended in the Amendment and Response filed on July 30, 2002, only refers to R¹ and R², *i.e.*, not R³, moieties. The definitions of R¹ and R² according to this claim do not appear to be inconsistent. In the event that the Amendment and Response, which was filed by facsimile, is not clearly legible, claim 17 as amended therein is reproduced below for Examiner's convenience:

17. (Amended) A compound according to Claim 1 wherein each R^a is hydrogen; R¹ is benzyloxycarbonyl; R² is aryl-X(CRR)_n-, aryl-(CRR)_n-, or cycloalkyl-(CRR)_n-; n is 1, 2, or 3; X is O or S; and R is hydrogen, methyl, or benzyl.

Finally, regarding claim 54, the Office Action notes that the claim defines "R⁷" but the formula in the claim does not include any such variable. As discussed above, the claims have been amended to remove references to this variable, and therefore this rejection is believed to be moot. Reconsideration of this rejection, as well as clarification and reconsideration of the other rejections under section 112, second paragraph, are respectfully requested.

Claim Rejections - 35 U.S.C. §102

Rejection of Claims 1, 2, 4, 5, 10, 18, 20, and 30 under 35 U.S.C. §102(b) over Dolle

The Office Action rejects claims 1, 2, 4, 5, 10, 18, 20, and 30 under 35 U.S.C. §102(b) over Dolle, *et al.* (EP 623,592), already of record. Without providing a specific rationale, the Office Action alleges generally that compounds 2 – 5, 9 – 16, 18, 20 – 21, 23, 25 – 27, and 30 – 32 anticipate these claims.

The disclosure of Dolle does not anticipate claim 1, or any of the claims 2, 4, 5, 10, 18, 20, or 30 that depend therefrom, because the cited reference does not disclose compounds having all of the features required by the instant claims.

A claim is anticipated only if a single prior art reference teaches expressly or inherently each and every element of the claimed invention. *Rowe v. Dror*, 112 F.3d 473, 478 (Fed. Cir. 1997). In other words, there must be no difference between the claimed invention and the

reference disclosure, as viewed by a person of ordinary skill in the art. *Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991).

All of the compounds of examples 2 – 5, 9 – 16, 18, 20 – 21, 23, 25 – 27, and 30 – 32 are β -tert-butyl esters of aspartic acid derivatives. Among other differences, the compounds of the present claims are all β -carboxylic acids of aspartic acid (see the $-\text{CO}_2\text{H}$ group of formula I of claim 1). Therefore, because all of the limitations of claim 1 and dependent claims are not taught by Dolle, the cited reference does not anticipate claim 1, 2, 4, 5, 10, 18, 20, or 30.

The cited reference does not teach any compounds within the scope of claims 1, 2, 4, 5, 10, 18, or 20, all of which are all directed to compounds. Claim 30 is directed to a pharmaceutically acceptable composition that contains a compound of claim 1. Where a compound *per se* is novel, it is axiomatic that any composition containing that same compound must also be novel. Accordingly, just as claim 1 is not anticipated by the instant cited reference, claim 30, which depends from claim 1 and is directed to a pharmaceutical composition comprising a compound of claim 1, is also not anticipated by the cited reference. Reconsideration of this rejection is respectfully requested. Indeed, to the extent that it is appropriate, these remarks pertaining to the novelty of pharmaceutical composition claim 30 apply equally to the other rejections under section 102 discussed below.

Rejection of Claims 1, 10, 11, and 30 under 35 U.S.C. §102(b) over Dolle

The Office Action also rejects claims 1, 10, 11, and 30 under 35 U.S.C. §102(b) over Mjalli, *et al.* (*Bioorg. Med. Chem. Lett.*, 1994), already of record. In support of such a rejection, the Office Action generally points to compound 3c, which is stated to be impliedly disclosed in the scheme depicted on page 1966 of the reference, and having the structure corresponding to “the *tert*-butyl ester of compound 4c.” Applicants traverse the rejection.

Although Applicants do not acquiesce to the Office Action’s conclusion that such a compound is disclosed by the reference with such specificity as to constitute an enabling prior art reference, even if such a compound is disclosed it would not anticipate the present claims. As discussed above regarding the Dolle reference, the present invention of claim 1 and the claims depending therefrom are directed to certain derivatives of aspartic acid. On the other hand, the

compound cited in the Office Action is a *tert*-butyl ester, which is outside of the scope of the present claims. In particular, the present claims are all directed to β -carboxylic acids, i.e., compounds having a $-\text{CO}_2\text{H}$ group, as illustrated in formula I of claim 1. This difference, among others, distinguishes these claims from the cited reference. As all of the limitations of the rejected claims are not met by the reference, they are not anticipated and reconsideration is requested.

Rejection of Claims 1, 10 – 11, 30, and 54 under 35 U.S.C. §102(b) over Thornberry

The Office Action also rejects claims 1, 10 – 11, 30, and 54 under 35 U.S.C. §102(b) over newly cited reference Thornberry, *et al.* (*Biochem.*, 1994). In particular, the Office Action cites compounds 1, 2, and 4 – 9 disclosed therein (presumably all of the compounds “4a – 9a” and “4b – 9b”). As explained below, the rejection is believed to be inapplicable. The indicated compounds of the cited reference do not anticipate the present claims.

Compounds 1 and 2 of Thornberry do not anticipate the present claims. Specifically, compounds 1 and 2 (illustrated in “Table 1” of the cited reference) are both aspartic acid derivatives in which the nitrogen atom of the aspartic acid is bound to an N-Ac-Tyr-Val- moiety. Although some of the compounds of the invention may indeed have a dipeptide R^1 group, the present claims do not embrace the compounds 1 or 2 of the reference. For example, such a moiety would require R^5 to be an N-Ac-Tyr group, which is equivalent to an R^{5a} acetyl group and an R^6 group corresponding to a hydroxybenzyl group, which is not permitted. Neither claim 1 nor claim 54 provide for such an R^6 group, and therefore these claims are not anticipated by the cited reference regarding compounds 1 and 2 therein. Because dependent claims fully incorporate the limitations of the claims from which they depend, compounds 1 and 2 of the cited reference would also not meet the limitations of dependent claims 10 – 11 and 30.

Furthermore, compounds 4a – 9a of Thornberry do not anticipate the present claims. These compounds, which are illustrated in “Table 2” of the cited reference, all relate to an aspartic acid derivatives in which the nitrogen atom is bonded to an alkylene group, namely an allyloxycarbonyl (“alloc”) group. In order for such compounds to fall within the scope of either claim 1 or claim 54, or any of the claims depending therefrom, R^1 would correspond to the

allyloxycarbonyl group, and consequently R³ would correspond to an allyl group (H₂C=CH-CH₂-), which contains a double carbon-carbon bond. The present claims make **no provision for such an alkylene R³ group**, and therefore the disclosure of compounds 4a – 9a does not anticipate any of claims 1, 10 – 11, 30, or 54.

Additionally, compounds 8a, 9a, 8b, and 9b of Thornberry do not anticipate the present claims. These compounds fall outside the scope of claims 1 and 54, and therefore claims depending therefrom, because the “Ar” groups (which correspond approximately to the R² groups of the present invention) **lack a carbonyl required by the present claims**. In contrast, the present claims require that the **R² group is bonded to a carbonyl group**, more particularly a carbonyloxy group, as depicted on the left-hand side of formula I of claims 1 and 54. As compounds 8a, 9a, 8b, and 9b do not possess the indicated carbonyl group, among other differences, the cited reference does not anticipate the pending claims.

Finally, compounds 4b – 7b of Thornberry do not anticipate the present claims. Claim 1 excludes compounds 4b and 7b specifically by name and is therefore not anticipated by the cited reference (compounds 4b and 7b correspond to “N-(N-phenylpropionyl-valinyl-alaninyl)-3-amino-4-oxo-5-(2,6-bis(trifluoromethyl)benzoyloxy) pentanoic acid and N-(N-phenylpropionyl-valinyl-alaninyl)-3-amino-4-oxo-5-benzoyloxy pentanoic acid). Regarding compounds 5b and 6b, the proviso of claim 1 has been amended to exclude these compounds specifically by name, and therefore claim 1 as amended is not anticipated by the cited reference with respect to these compounds.

Indeed, none of the compounds 1 – 2, 4a – 9a, or 4b – 9b anticipates the present invention. In view of the foregoing, Applicants assert that claim 1 as amended herein as well as claims depending therefrom, in addition to claim 54, are not anticipated by Thornberry, and reconsideration of the instant rejection is respectfully requested.

Rejection of Claims 1, 10 – 11, 30, and 54 under 35 U.S.C. §102(b) over Chapman

The Office Action also rejects claims 1, 10 – 11, 30, and 54 under 35 U.S.C. §102(b) over Chapman, *et al.* (U.S. 5,430,128), already of record. In particular, the Office Action cites

three compounds disclosed at col.8, ll.23-29, and the passage at col.14 – col.18 describing the chemical synthesis of these three compounds. The three compounds disclosed in this reference are (a) N-(N-phenylpropionyl-valinyl-alaninyl)-3-amino-4-oxo-5-(2,6-bis(trifluoromethyl)benzoyloxy) pentanoic acid; (b) N-(N-phenylpropionyl-valinyl-alaninyl)-3-amino-4-oxo-5-benzoyloxy pentanoic acid; and (c) N-(N-acetyl-tyrosinyl-valinyl-alaninyl)-3-amino-4-oxo-5-(pentafluorobenzoyloxy) pentanoic acid. These three compounds, and indeed none of the compounds of Chapman, are not within the scope of claims 1, 10 – 11, 30, or 54.

Regarding claim 1, these three compounds are specifically recited in the proviso, and therefore claim 1 is novel with respect to this reference. Furthermore, as dependent claims incorporate all of the limitations of the claims from which they depend, claims 10 – 11 and 30 are also novel with respect to this reference.

Regarding claim 54, compound “a” has an **R² group corresponding to a (CF₃)₂-phenyl-** group [compound “a” is N-(N-phenylpropionyl-valinyl-alaninyl)-3-amino-4-oxo-5-(2,6-bis(trifluoromethyl)benzoyloxy) pentanoic acid]. Likewise, compound “c” has a **R² group corresponding to a F₅-phenyl-** group [compound “c” is N-(N-acetyl-tyrosinyl-valinyl-alaninyl)-3-amino-4-oxo-5-(pentafluorobenzoyloxy) pentanoic acid]. Claim 54 does not include such fluoro- or trifluoromethyl-substituted R² phenyl groups. Therefore, the teachings of the cited reference regarding these compounds do not anticipate claim 54. Claim 54 is not anticipated by the cited reference with regard to the disclosure of compounds “a” and “c”.

Furthermore, the three compounds of the cited reference do not anticipate claim 54 regarding the corresponding R¹ groups of those compounds. Compounds “a” and “b” both contain an R¹ group corresponding to N-phenylpropionyl-valinyl-alaninyl, which according to the language of the claims corresponds to an alaninyl group and an R⁵ subunit corresponding to N-phenylpropionyl-valinyl. The R⁵ group itself is further directed to a valinyl group and an **R^{5a} subunit, which is not permitted,** having the structure N-phenylpropionyl (*i.e.*, **-(C=O)-CH₂-CH₂-phenyl**). Claim 54 makes no provision for such an R^{5a} group. That is, R^{5a} groups having the structure -(C=O)-(CH₂)_n-aryl are not included within the scope of claim 54, and this claim is therefore not anticipated.

In brief, Chapman does not teach any compounds that are within the scope of the instant rejected claims. As such, the rejected claims are not anticipated by the cited reference, and reconsideration of this rejection is respectfully requested.

Rejection of Claims 1, 10, 16, 21, 30, and 54 under 35 U.S.C. §102(b) over Heng

Finally, the Office Action rejects claims 1, 10, 16, 21, 30, and 54 under 35 U.S.C. §102(b) over Heng, *et al.* (EP 618,223), already of record. The Office Action alleges that claims 1, 10, 16, 21, 30, and 54 are anticipated by the disclosure of compounds 31, 43 – 45, 48 – 55, 58 – 63, 79 – 86, and 90 – 91 disclosed therein. Applicants, however, disagree.

Regarding claim 1 and claims depending therefrom, compounds 31, 43, 50, 52, 54, 81, 82, 86, and 90 are disclaimed by name in the proviso appearing at the end of the claim. Therefore, with respect to these compounds, claim 1 is novel.

Certain of the compounds of the cited reference are β -alkyl esters of aspartic acid derivatives. Among other differences, the compounds of the present **claims are all β -carboxylic acids** of aspartic acid (see the **-CO₂H group** of formula I of claim 1). Claim 1, as well as the claims depending therefrom, and claim 54 all recite the generic chemical structure of formula I that requires a -CO₂H group. Specifically, compounds 45, 48 – 49, 53, 59, 63, 79, 80, and 85 are all ethyl esters of aspartic acid having a **-CO₂CH₂CH₃ group instead of the -CO₂H group required by** formula I of claims 1 and 54. Accordingly, compounds 45, 48 – 49, 53, 59, 63, 79, 80, and 85 do not anticipate claim 1 (and dependent claims) or claim 54. Likewise, compounds 44, 51, 55, 60, 62, 84, and 91 are all *tert*-butyl esters of aspartic acid having a **-CO₂C(CH₃)₃ group instead of the -CO₂H group required by** formula I of claims 1 and 54. Accordingly, for these reasons and others, compounds 44, 51, 55, 60, 62, 84, and 91 do not anticipate claim 1 (and dependent claims) or claim 54.

Compounds 58 and 61 of Heng have non-amino acid groups in positions A₃ and A₄, respectively, and the present claims make no provision for such groups. Indeed, none of the compounds, as disclosed in the cited reference anticipate claim 1 as explained above. Furthermore, none of the compounds anticipates claim 54, as explained further below.

Regarding claim 54, the moiety described in the reference on p.10 as Z-A₃-A₄- corresponds to an R¹ group of the generic formula I of claim 1. This group corresponds to an A₄ amino acid bonded to an R⁵ group (equaling the remaining Z-A₃- moiety). This R⁵ group therefore corresponds to an A₃ amino acid and an R^{5a} group (equaling the remaining Z- moiety). That is, in order for the compounds of the cited reference to fall within the scope of claim 54, *at least* R^{5a} must embrace a Z group. The Z group is defined at p.9, l.36 of the cited reference as a benzyloxycarbonyl group, *i.e.*, -(C=O)-O-CH₂-phenyl, which is not permitted by claim 54. In other words, claim 54 makes no provision for such an R^{5a} group. More specifically, R^{5a} groups having the structure -(C=O)-O-(CH₂)_n-aryl are not included within the scope of claim 54. Referring to the compounds disclosed by the cited reference, compounds 31, 43 – 45, 48 – 55, 58 – 63, 79 – 86, and 90 – 91 have such an R^{5a} benzyloxycarbonyl group, and therefore these compounds do not anticipate claim 54.

Additionally concerning claim 54, compounds 43 – 45, 48 – 55, 58 – 63, 79 – 86, and 90 – 91 all have an R² group corresponding to a 1,6-dichlorophenyl group (“Za” of the disclosure corresponds to a -O₂CR² group according to formula I of claim 1). As discussed above, 1,6-dichlorophenyl-substituted R² groups are not included within the scope of claim 54. Therefore, among other reasons, the teachings of the cited reference regarding these compounds does not anticipate claim 54. Indeed, none of the cited compounds falls within the scope of the present claim 54.

In summary, none of the references Dolle, Mjalli, Thornberry (first made of record in the present Office Action), Chapman, or Heng, cited under section 102 discloses, explicitly or inherently, all of the features of the present claims, and therefore none of these references anticipates the pending claims. Accordingly, reconsideration of the rejection of the claims for anticipation by the cited references and allowance of the pending claims is earnestly sought.

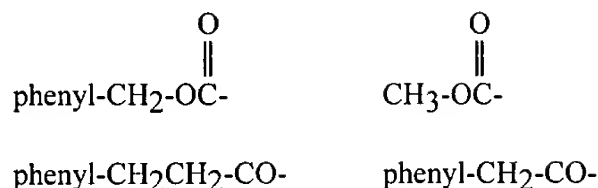
Claim Rejections - 35 U.S.C. §103

Although the references cited under section 103(a), discussed below, teach specific ICE inhibitors and related compounds, none of the references explicitly or implicitly suggests that particular structural features of the distinct ICE inhibitors should be combined in the specific pattern recited in the instant claims. In other words, the cited references, alone or in combination, neither teach nor suggest that a particular first element of the ICE inhibitors of one reference should be combined with a particular second element of the ICE inhibitors of another reference to arrive at the compounds recited by the instant claims.

Rejection of Claims 1, 2, 4, 5, 8, 10 – 12, 21, 23 – 27, 30, and 52 – 54 under 35 U.S.C. §103(a) over Chapman

In the pending Office Action, claims 1, 2, 4, 5, 8, 10 – 12, 21, 23 – 27, 30, and 52 – 54 under 35 U.S.C. §103(a) as unpatentable over Chapman, *et al.* (U.S. 5,430,128). Several distinguishing features of the present invention over Chapman are discussed above with respect to the corresponding rejection under section 102(b), and the substance of those remarks are reiterated herein.

Regarding claims 2, 4, 5, and 8, the Office Action states that Chapman “exemplifies only an alloc group” as R¹, namely the group H₂C=CH-CH₂-O-CO-. The Office Action further states that the R¹ groups of claims 2, 4, 5, and 8 “are amino acid protection groups known in the art. It would have been obvious . . . to substitute any known amino acid protecting group Variation of protecting groups is within the scope of the artisan.” Claims 2, 4, 5, and 8 are directed solely to compounds having the following four R¹ groups:



In order to establish a *prima facie* showing of obviousness over the prior art, the Examiner must show the following three elements: (1) a suggestion or motivation to combine or modify the cited references; (2) a reasonable expectation of success; and (3) that the combination or modification of the prior art references teaches all the limitations of the claim at issue. Failure to show any one of the foregoing negates a *prima facie* showing. The initial burden is on the Examiner to provide some suggestion of the desirability of doing what the inventor has done. M.P.E.P. §2142 *et seq.*

Whether the rejection for obviousness depends on a combination of prior art references or a single reference alone, there must be some teaching, suggestion, or motivation to combine or modify the references. Usually, the suggestion comes from the teachings of the pertinent references, or from the ordinary knowledge of those skilled in the art that certain references are of special importance. Therefore, when examining the patentability of a claimed invention that combines known elements, “the question is **whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination.**” *In re Rouffet*, 149 F.3d 1350, 1355-56 (Fed. Cir. 1998) (emphasis added); *see also*, *GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1462 (Fed. Cir. 1984); and *In re Beattie*, 974 F.2d 1309, 1311-12 (Fed. Cir. 1992). In other words, it not sufficient that the prior art could be so modified. Rather, the prior art must teach or suggest that the prior art should be modified. *See, In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984).

Merely identifying all of the elements of a claim or their equivalents in the prior art is not sufficient. Almost all inventions are combinations of old elements, and an examiner may often find every element of a claimed invention in the prior art. If this finding were sufficient “to negate patentability, very few patents would ever issue.” *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998). Therefore, in order to establish a *prima facie* rejection for obviousness, an “examiner must show reasons that the skilled artisan, confronted with the same problems as the

inventor and with no knowledge of the claimed invention, would [*not* could] select the elements from the cited prior art references for combination in the manner claimed.” *Id.*

Turning to the present rejection of claims 2, 4, 5, and 8, Applicants submit that the Office Action has failed to provide a reasoned statement why one skilled in the art would have modified the teachings of Chapman to arrive at the present invention. First, the Office Action sites no prior art reference in support of its allegation that the alloc group of the compound of Chapman is a “protecting group” and the groups of claims 2, 4, 5, and 8 are also protecting groups. Assuming that the Office Action relies on such knowledge as being commonly known to one skilled in the art, the Office Action provides no explanation of how one skilled in the art would have been motivated to make such a modification of the teachings of the cited reference. An informal search of U.S. patents since 1976 indicates that over 20,000 patents relate to the chemistry of a great number of different “protecting groups.” The Office Action makes no showing of which of the multitude of protecting groups would be an appropriate variation of an alloc group.

Assuming that such a prior art reference could be cited, the Office Action shows no motivation to combine the teachings of Chapman and such a hypothetical prior art reference to arrive at the particular embodiments represented by claims 2, 4, 5, and 8. As discussed above, it is not sufficient to show that certain claim elements may be found in the prior art; rather, in order to establish a *prima facie* obviousness rejection, the direction that one *should* modify the prior art in order to arrive at the claimed invention must be specifically suggested by the prior art itself. The Office Action makes no such showing, other than a vague allegation that the groups of claims 2, 4, 5, and 8 are protecting groups like the alloc group of Chapman.

In addition to the chemical differences between the Chapman compound and the present invention, the hypothetical missing prior art citation would have to show not only the desirability of modifying the Chapman compound chemically, but also address the different utility of the Chapman compounds and suggest a reason for using the Chapman compounds for a different purpose. The compounds of the invention embodied by the present claims are useful as enzyme inhibitors and as pharmaceuticals. In contrast, the utility of the compound cited in Chapman is as an intermediate in a chemical synthesis, the end product of which is an enzyme inhibitor. As such, this compound includes a “protecting group.”

Applicants submit that a “protecting group” is generally known to be a chemical moiety used in a synthetic chemistry protocol to temporarily mask the reactivity of a functional group. In the context of Chapman, the term “protecting group” could only be used to describe features of compounds that are used as intermediates in the synthesis of other compounds.

Typically, protecting groups are removed once the synthesis is completed. In fact, the end product of the synthesis disclosed in Chapman is an ICE inhibitor and is devoid of the protecting group that was present on the intermediate compound cited by Examiner. In other words, the alloc group of the intermediate was removed prior to produce the final product. Therefore, based on this teaching, one skilled in the art would have no motivation to modify the biologically active end products of Chapman by addition of a protecting group. Moreover, Chapman does not disclose modifying the biologically active compounds by addition of any particular protecting group. Indeed, the disclosure of Chapman constitutes a clear teaching away from the claimed invention.

Moreover, the compounds of the invention are compounds having enzyme inhibiting activities and as such are useful as pharmaceuticals. That is, the present invention relates to compounds that one skilled in the relevant art would not ordinarily consider to be useful as materials for use in the synthesis of other molecules as intermediates, but rather chemical compounds with a medicinal use. Therefore, the Office Action has simply not established a motivation to combine the teachings of Chapman with the “prior art.”

Because the Office Action does not provide a rationale for why one skilled in the art would have been motivated to combine the teachings of Chapman with those of the prior art, notwithstanding the absence of a specific citation to a prior art reference providing appropriate complementary teachings, a *prima facie* case of obviousness is not established. Furthermore, the Office Action does not give a reason why one skilled in the art would arrive at the present invention relating to enzyme inhibitors, given the disclosure of the cited compound of Chapman having utility as a synthetic chemistry intermediate; and a *prima facie* obviousness rejection is all the more inadequate.

Regarding claim 12, in which R² is $-(CH_2)_n$ -naphthyl, the Office Action summarily states that although the cited reference does not disclose such a naphthyl group, one skilled in the art would expect a naphthyl group to have similar activity in view of the disclosure in this

position of a phenyl group (disclosed in a list of the numerous other moieties at col.3-4). The cited passage in Chapman at col.3-4 discloses lengthy lists of the possible substituents of the moieties. For example, Chapman at col.4, l.7, describes “mono, di or trisubstituted aryl” groups, which may be substituted with any moiety selected from a list of 27 different classes of substituents. The Office Action gives no explanation of why one would be motivated to select only an *unsubstituted* aryl group from these lists, or why that aryl group should be a naphthyl group. The Office Action proffers **no prior art** evidence in support of the alleged interchangeability of such naphthyl and phenyl groups. Furthermore, the Office Action does not provide a rationale for why one skilled in the art would have been **motivated to select the phenyl group** from the multitude of other groups disclosed in the Chapman reference, **let alone combine the teachings** regarding that phenyl group with a hypothetical prior art citation to change the phenyl group to a naphthyl group. Accordingly, a *prima facie* case of obviousness has not been established for this claim.

Claims 21 and 23 – 27, relating to method of using the compounds of the invention in the treatment of subjects or inhibition of certain enzymes, are rejected in the Office Action as obvious over Chapman. In support of this rejection, the Office Action refers to four passages in the patent. Inasmuch as these method claims depend from compound claims, the patentability of which has been addressed above, the substance of those remarks are reiterated herein with respect to these claims. These claims also include a further limitation, namely the particular recited use, and, therefore, are all the more novel and nonobvious over the cited reference. Furthermore, regarding claim 23, which pertains to a method of treating stroke, Chapman makes no disclosure whatsoever regarding the **treatment of stroke**, and the Office Action provides no explanation of how the teachings of Chapman could be modified in this regard to arrive at the present invention. Additionally, claim 26 specifically relates to the **treatment of inflammatory bowel disease**, which is not addressed whatsoever by Chapman. Indeed, respecting all of claims 21 and 23 – 27, the Office Action **cites only Chapman itself and no additional reference providing the additional teachings** necessary to arrive at the present invention. The Office Action merely makes reference to “ordinary skill in the art,” and provides **no explanation why the prior art itself suggests the desirability of any combination of prior art teachings** to arrive at the present invention, other than a summary conclusion that the invention would have

been obvious. Therefore, Applicants assert that a proper *prima facie* case of obviousness has not been set forth.

Regarding claims 52 and 53, the Office Action correctly notes that the compounds disclosed in Chapman do not anticipate these claims because they each are limited to compounds having R^{5a} groups *not* equaling N-phenylpropionyl (*i.e.*, -(C=O)-CH₂-CH₂-phenyl). The Office Action nevertheless rejects these claims as obvious over Chapman. In support of the obviousness rejection, the Office Action states that the R^{5a} moiety of the present claims corresponds to the R₁ moiety of Chapman where AA₁ is a single bond. The Office Action merely indicates that at the time of invention it would have been obvious to substitute “*any moiety* in the definition of R₁” (emphasis added), without any explanation whatsoever. That is, the Office Action provides no comparison of the teaching of Chapman with the claimed invention, **no cited prior art reference** which in combination with the teachings of Chapman, would theoretically disclose **all of the limitations** of the claimed invention, **no explanation of a suggestion or motivation to combine** Chapman with the teachings of such a prior art reference, and **no rationale regarding a reasonable expectation of success**. Examiner has accordingly not satisfied the initial burden of establishing a *prima facie* case of obviousness regarding this rejection.

Similarly, “claims 1 and 52 – 54 in general” are rejected in the instant Office Action for obviousness over Chapman. The Office Action states in conclusory language that although Chapman “exemplified a limited set of compounds[, it] expressly suggests the preparation of many more compounds via simple change” of the moieties comprising the generic chemical structures disclosed in the reference. It appears that the Office Action seeks to establish a rejection of the generic claims in the present application over a hypothetical genus not actually disclosed in the prior art. However, the Office Action cites nothing in Chapman or any other reference that sets forth the available choices for the “simple change,” or which among the available choices should be selected to arrive at the instant invention. Accordingly, Chapman does not teach or suggest all the elements of the present claims. Consequently, Chapman does not, *indeed cannot*, provide the requisite motivation to one skilled in the art to select the compounds of the invention to be prepared via “simple change.” A *prima facie* obviousness rejection has not been established.

The caption of this section of the Office Action at the bottom of page 5 states that claims 10 – 11 and 30 are also subject to rejection under 35 U.S.C. §103(a) as unpatentable over Chapman. However, the Office Action provides no specific explanation of the grounds for the rejection of these claims. Therefore, these claims have not been specifically addressed in this section. Applicants nevertheless believe that the present Amendment and Response is fully responsive to the pending Office Action. To the extent that the above remarks are deemed not to address the specific objections/rejections contemplated by Examiner, Applicants respectfully request further clarification of the status of these claims. Indeed, as the above remarks are believed to fully address the rejection of all claims as obvious over Chapman, reconsideration of the rejection of all of these claims is respectfully requested.

Rejection of Claims 1, 10 – 12, 16, 21, 24 – 28, 30, and 52 - 54 under 35 U.S.C. §103(a) over Heng; Claim 22 over Heng in view of Spruce; and Claim 29 over Heng in view of Bemis

In the pending Office Action, claims 1, 10 – 12, 16, 21, 24 – 28, 30, and 52 – 54 are rejected under 35 U.S.C. §103(a) as unpatentable over Heng, *et al.* (EP 618,223). Claim 22 is also rejected under 35 U.S.C. §103(a) as unpatentable over Heng in view of newly cited reference Spruce, *et al.* (U.S. 6,004,933). Also, Claim 29 is rejected under 35 U.S.C. §103(a) as unpatentable over Heng in view of newly cited reference Bemis, *et al.* (U.S. 5,843,904). Some of the features of the present invention that impart novelty over the disclosure of Heng are discussed above regarding rejections to the claims under section 102(b) and, to the extent that they are relevant here, the substance of those remarks are reiterated herein.

Regarding claims 11 and 12, in which R² is defined as -(CH₂)_n-phenyl and -(CH₂)_n-naphthyl, respectively, the Office Action states that Heng “expressly suggests” that the groups corresponding to the R² groups of the present invention may be an “unsubstituted phenyl or naphthyl.” No explanation of the alleged express suggestion is proffered in the Office Action. The 97 example compounds of Heng do not include any compounds whatsoever having an R² group corresponding to a unsubstituted aryl group, let alone an unsubstituted phenyl or naphthyl group (“Za” of the disclosure corresponds to a -O₂CR² group according to formula I of claim 1). Furthermore, none of the 97 example compounds have a naphthyl-containing R²

group, substituted or unsubstituted. Applicants find **no basis for the allegation** that Heng implicitly discloses R^2 groups defined as $-(CH_2)_n$ -phenyl and $-(CH_2)_n$ -naphthyl, nor has the Office Action set forth any rationale for such an allegation. As the initial burden is on Examiner to provide some suggestion of the desirability of doing what the inventor has done as evidenced by citations to the prior art, a proper *prima facie* rejection has not been established.

Claims 24 – 26 and 28, relating to method of using the compounds of the invention in the treatment of subjects with various diseases or conditions, are rejected in the Office Action as obvious over Heng. In support of this rejection, the Office Action refers to the passage bridging pp.19-20. Inasmuch as these method claims depend from compound claims, the patentability of which has been addressed above, the substance of those remarks are reiterated herein with respect to these method claims. And as these claims include a further limitation, namely the particular recited use, these claims are all the more novel and nonobvious over the cited reference.

Respecting claims 52 and 53, the Office Action correctly notes that the compounds disclosed in Heng do not anticipate these claims because they each are limited to compounds having R^{5a} groups *not* equaling N-phenylpropionyl (*i.e.*, $-(C=O)-CH_2-CH_2$ -phenyl), although as explained elsewhere herein other features distinguish the present invention from Heng. The Office Action nevertheless rejects these claims as obvious over Heng. In support of this obviousness rejection, the Office Action states that the R^{5a} moiety of the present claims corresponds to the R moiety of Heng. The Office Action then refers to a passage at p.4 in Heng reciting a variety of possible R groups. Although the R^{5a} moieties of the present claims may be found as elements in the definition of the “R group” of Heng, the present invention is in no way obvious over the disclosure of Heng.

As explained more fully above, **merely identifying the an element of a claim in the prior art is not sufficient to establish a proper *prima facie* rejection**, because nearly all inventions, which are almost totally combinations of old elements, would be obvious. In order to establish a *prima facie* rejection for obviousness, an “examiner must show reasons that the skilled artisan . . . would [*not could*] select the elements from the cited prior art references for combination in the manner claimed.” *In re Rouffet, supra*.

Accordingly, the Examiner must show a motivation to modify the teachings of the Heng reference itself to select the particular elements to arrive at the claimed invention, or to combine Heng with another reference teaching the additional subject matter not disclosed by Heng that would be required to meet all of the claim limitations, a reasonable expectation of success upon combining those teachings, and that the combination teaches *all* the limitations of claim 52 and 53. Such a showing has not been made in the present rejection, *e.g.*, Examiner has not addressed how the other claim elements of claims 52 and 53 would be met by Heng. A proper *prima facie* rejection has not been set forth for claims 52 and 53.

Similarly, "claims 1 and 52 – 54 in general" are rejected in the Office Action over Heng. The Office Action states in conclusory language that the reference "expressly suggests the preparation of many more compounds via simple change" of the moieties comprising the generic chemical structures disclosed in the reference. It appears that the Office Action again seeks to establish another rejection of the generic claims in the present application over a hypothetical genus not actually disclosed in the prior art. Applicants respectfully traverse inasmuch as the Office Action provides no cited prior art references, no explanation of motivation to combine such references with Heng nor a rationale regarding a reasonable expectation of success upon such combination. Accordingly, a *prima facie* obviousness rejection has not been established respecting these claims.

Claim 22 is also rejected under 35 U.S.C. §103(a) as unpatentable over Heng in view of newly cited reference Spruce, which is relied on as teaching that "ICE is a member of the caspase family and that caspase enzymes are implicated in the same diseases as ICE." Applicants submit that Spruce is not applicable prior art. The Spruce patent was granted (*i.e.*, published) on December 21, 1999, from an application filed on April 23, 1998 (with a priority claim to April 25, 1997). Therefore, the effective date of this reference under 35 U.S.C. §102(a)-(b) is December 21, 1999, and the effective date of this reference under 35 U.S.C. §102(e) is April 25, 1997.

The instant application is a U.S. national phase application filed pursuant to 35 U.S.C. 371 from a PCT application filed October 9, 1997 (with a priority claim to October 11, 1996). This application is entitled to the filing date of October 9, 1997 for the material disclosed in the PCT application as filed. The October 9, 1997, filing date precedes the effective date of Spruce

under §102(a) and (b). The October 11, 1996, priority date precedes the effective date of Spruce under §102(e). Therefore, Spruce is not prior art under §103(a).

Claim 29, directed to a method of treating shigellosis, is rejected under 35 U.S.C. §103(a) as unpatentable over Heng in view of newly cited reference Bemis, which is relied on as teaching that "ICE inhibitors have utility in the treatment of shigellosis." Inasmuch as this method claim depends from compound claim 1, the patentability of which has been extensively addressed above, the substance of those remarks are reiterated herein with respect to this method claim. And as claim 29 includes a further limitation, namely the particular recited use, this claim is all the more novel and nonobvious over the additional cited reference.

The caption of the section of the Office Action at the middle of page 7 states that claims 16, 21, 27, and 30 are also subject to rejection under 35 U.S.C. §103(a) as unpatentable over Heng. However, the Office Action provides no specific explanation of the grounds for the rejection of these claims. Therefore, these claims have not been specifically addressed in this section. Applicants nevertheless believe that the present Amendment and Response is fully responsive to the outstanding Office Action. To the extent that the above remarks are deemed not to address the specific objections/rejections contemplated by Examiner, Applicants respectfully request further clarification of the status of these claims. Indeed, as the above remarks are believed to fully address the rejection of all claims rejected as obvious over Heng alone or in combination with Spruce or Bemis, reconsideration of the rejection of all of these claims is respectfully requested.

Rejection of Claims 1, 2, 4 – 8, 10 – 12, 17 – 18, 20, 30, and 52 – 54 under 35 U.S.C. §103(a) over Dolle; and Claims 1, 21, 24 – 28, and 52 – 54 over Dolle in view of Heng

The Office Action states that claims 1, 2, 4 – 8, 10 – 12, 17 – 18, 20, 30, and 52 – 54 are rejected under 35 U.S.C. §103(a) as unpatentable over Dolle, *et al.* (EP 623,592). The Office Action also states that claims 1, 21, 24 – 28, and 52 – 54 are rejected under 35 U.S.C. §103(a) as unpatentable over Dolle in view of Heng (discussed above). The Office Action provides a reasoned statement for the rejection of a different group of claims, namely claims 1, 6 – 8, 11 – 12, 17, 21, 24 – 28, and 52 – 54, and the remarks below are directed to these claims. To the extent that these remarks are deemed not to address the specific objections/rejections

contemplated by Examiner, Applicants respectfully request further clarification of precisely which claims stand rejected over Dolle.

The Office Action rejects claims 6 and 7 as obvious over Dolle. Claims 6 and 7 are directed to compounds in which R¹ is N-acetyl-alanine and N-acetyl-valine, respectively. In particular, the Office Action states that while the reference does not specifically exemplify compounds having R¹ equal to N-acetyl-alanine or N-acetyl-valine, it would have been obvious to substitute any well-known amino acid protecting group, such as acetyl, and such substitution is suggested by the reference by the use of different protecting groups in the examples. The Office Action specifically points to examples 18 and 23 as supportive of the basis for the present rejection. Example compounds 18 and 23 are, respectively, N-methoxycarbonyl-L-alanine-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone β -*tert*-butyl ester and N-methoxycarbonyl-L-valine-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone β -*tert*-butyl ester.

As explained above more fully, the following three elements must exist in order to establish a *prima facie* showing of obviousness over a prior art reference: (1) a suggestion or motivation to modify the cited reference; (2) a reasonable expectation of success; and (3) that the reference teaches all the limitations of the claim at issue.

In rejecting claims 6 and 7, the Office Action argues that the teachings of Dolle with respect to examples 18 and 23 therein may be modified by substitution of the methoxy carbonyl group for an acetyl group. Such a modification of compounds 18 and 23 would not place them within the scope of claims 6 or 7. The Office Action has not provided a prior art reference evidencing the interchangeability of methoxycarbonyl and acetyl groups. Instead, the Office Action makes vague reference to general knowledge in the art instead of specifically addressing the required showing of motivation to modify and expectation of success. Even assuming, for the sake of argument, that such a reference were available and that it has been properly applied according to the mandatory three-part test quoted above and articulated by the Court of Appeals for the Federal Circuit, the proposed modification would not teach all of the limitations of the rejected claims. That is, if the Office Action had shown, continuing the hypothetical argument, that one could substitute a methoxy carbonyl group for an acetyl group, the compound so modified would not fall within the scope of claims 6 or 7. In particular, attention is drawn to the fact that example compounds 18 and 23 are β -*tert*-butyl esters, whereas claims 6 and 7 are drawn

to carboxylic acid compounds (by incorporation of the limitations of claim 1). Accordingly, a *prima facie* obviousness rejection of claims 6 and 7 has not been properly set forth.

Likewise, in rejecting claim 8, drawn to compounds in which R¹ is phenyl-CH₂-CO-, the Office Action argues that the teachings of Dolle may be modified analogously as proposed for claims 6 and 7 discussed immediately above. The Office Action, however, does not provide any specific examples, of how the teachings of Dolle are to be modified. Absent such detail, the Office Action has not satisfied its burden of initially establishing a *prima facie* case of obviousness. As illustrated in extensively detailed analysis immediately above with respect to claims 6 and 7, the random substitution of various portions of the molecules of the cited references does not necessarily render the invention obvious.

Claims 11 – 12, 17, and 52 – 54 are rejected as being obvious over unspecified compounds of Dolle that allegedly have “substituted phenyl groups.” The Office Action further states that it would have been obvious to modify the teaching of Dolle to replace these “substituted phenyl groups” with an “unsubstituted phenyl or naphthyl at this position” and thereby arrive at the invention of the claims. The Office Action, however, fails to set forth a proper showing of *prima facie* obviousness.

As explained above, it is the burden of Examiner to show how the reference teaches all the limitations of the claim at issue, let alone how those the reference itself suggests a modification to arrive at the present invention. Although claims 11 and 12, for example, state that R² are -(CH₂)_n-phenyl or -(CH₂)_n-naphthyl, claims 11 and 12 depend from claim 1 and therefore also incorporate all of the limitations of claim 1. That is, although it is not stated explicitly, the subject matter of claims 11 and 12 also have R¹ substituents in addition to R² substituents. The Office Action offers no explanation of how the proposed modification of Dolle would meet *all* of the claim limitations of any of claims 11 – 12, 17, or 52 – 54, and therefore does not establish a legal showing of *prima facie* obviousness.

Claims 1, 21, 24 – 28, and 52 – 54 are also rejected under 35 U.S.C. §103(a) as unpatentable over Dolle in view of Heng. The Office Action relies on Deng as teaching compounds that are “immediate precursors to the equivalent carboxylic acid” that admittedly do

not have "therapeutic activity," and it relies on Heng for the further teaching that "pro-drugs, such as esters and amides, have utility as ICE inhibitors."

As discussed in detail above, the Office Action proffers no rationale by which the teachings of Dolle may be specifically modified to arrive at the present invention as defined by all of the limitations of the present claims. Those remarks are reiterated herein, and to the extent that the attempted showing of obviousness is deficient as explained above, it is all the more deficient with respect to claims 1, 21, 24 – 28, and 52 – 54 as they relate to "esters, amides, and prodrugs thereof."

The Office Action also relies on Dolle for a teaching that is not disclosed in the reference. The Office Action admits that the compounds of Dolle that serve as a basis for the present rejection are "[i]ntermediate compounds for use in making the final compounds" (p.12, ll.55). That is, the compounds are useful as source materials for the preparation of other compounds, "synthetic intermediates." The present invention relates to compounds having a medicinal use. Stated alternatively, the Office Action relies on Dolle for a teaching that is non-analogous to the general subject matter of the present invention. No explanation is provided by the Office Action for why one skilled in the art would have been motivated to modify the Dolle compounds disclosed as being useful chemical reagents to arrive at the medicinal compounds of the present invention (let alone why one would have also been motivated to make the requisite modifications to the chemical structures of the compounds). Accordingly, a *prima facie* showing of obviousness has not been established.

Allowed and Allowable Subject Matter

Applicants acknowledge and sincerely thank Examiner for her determination that claims 34, 38 – 41, and 44 – 51 are allowed, and that claims 3, 13 – 15, and 19 would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. However, on page 6 of the Office Action dated October 25, 1999 (Paper No. 4), Examiner previously indicated that in addition to the claims listed above, claims 8, 12, 17, and 20 – 23 would also be allowable if properly rewritten in independent form. Applicants respectfully and earnestly request that the claims previously found to be allowable, yet subject to rejection or objection herein, be presently allowed.

CONCLUSION

In view of foregoing, entry of the amendments and remarks presented herein, favorable reconsideration and withdrawal of all rejections and objections, and allowance of this application with all the claims as amended herein are respectfully solicited. Cancellation of or amendments to the claims should in no way be construed as an acquiescence to any of Examiner's objections or rejections. Such cancellation or amendment of the claims is being made solely to expedite prosecution of this application. Applicants reserve the option to further prosecute the same or similar claims in the present or another patent application.

A request for a one-month extension of time pursuant to 37 C.F.R. §1.136(a) is submitted herewith. No additional extension of time is believed to be necessary. However, if such an extension of time should be required, then Applicants hereby request an extension of time and authorize the Commissioner to charge the associated fee to our Deposit Account No. 12-0080. Also, please charge the fee of \$126.00 for seven excess claims (representing new claims 55 – 61 added herein) to our Deposit Account No. 12-0080. If any additional fees are due, then please charge our Deposit Account No. 12-0080.

If there are any remaining issues or Examiner believes that a telephone conversation with the Applicants' attorney would be helpful in expediting prosecution of this application, Examiner is invited to call the attorney of record at (617) 227-7400.

Respectfully submitted,

LAHIVE & COCKFIELD, LLP

Dated: Jan 29, 2003

By: 

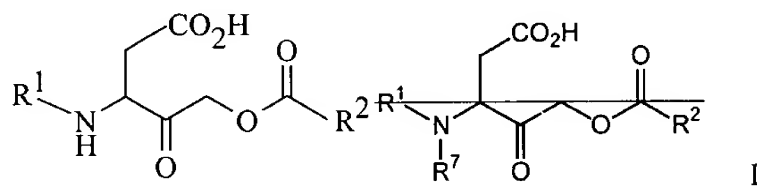
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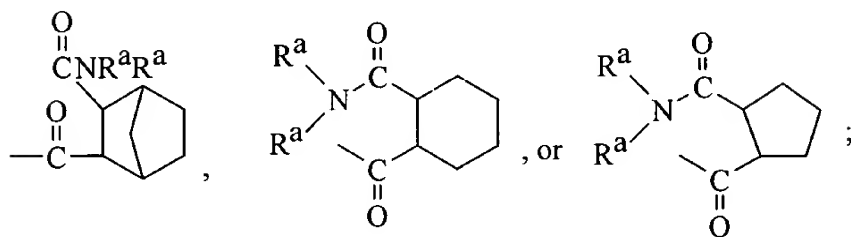
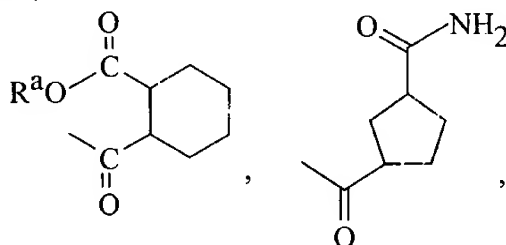
APPENDIX

Version with Markings to Show Changes Made

- (Amended Four Times) A compound of the Formula I

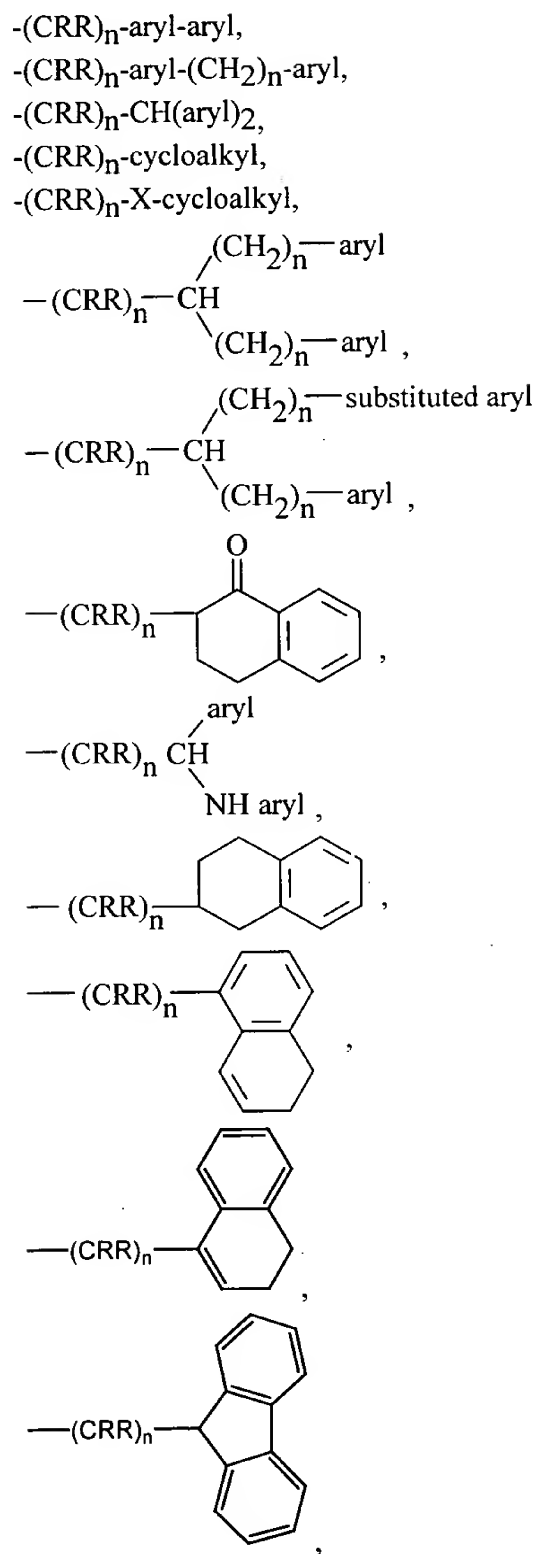


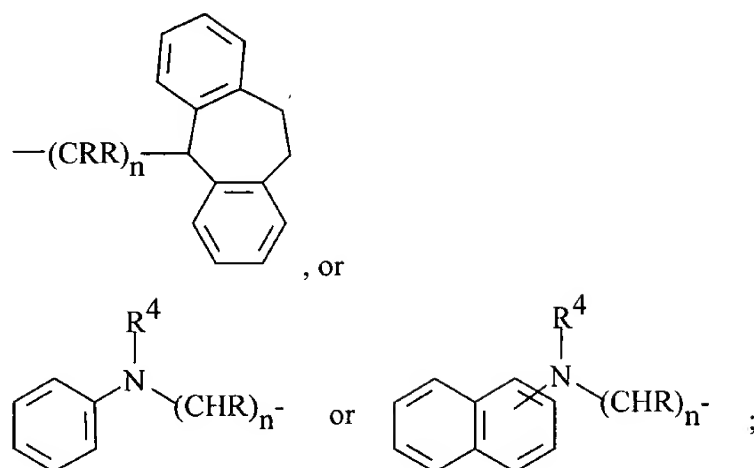
wherein R^1 is $R^3OC(=O)-$,
 R^3CO- ,
 R^3SO_2- ,
 R^a
 $|$
 $R^5NCH(R^6)CO-$,



each R^a is independently hydrogen, C_1-C_6 alkyl, or $-(CH_2)_n$ aryl;

R^2 is $-(CRR)_n$ -aryl,
 $-(CRR)_n$ -X-aryl,
 $-(CRR)_n$ -(substituted-aryl),
 $-(CRR)_n$ -X-(substituted-aryl),





each R is independently hydrogen, C₁-C₆ alkyl, halogen or hydroxy;

X is O or S;

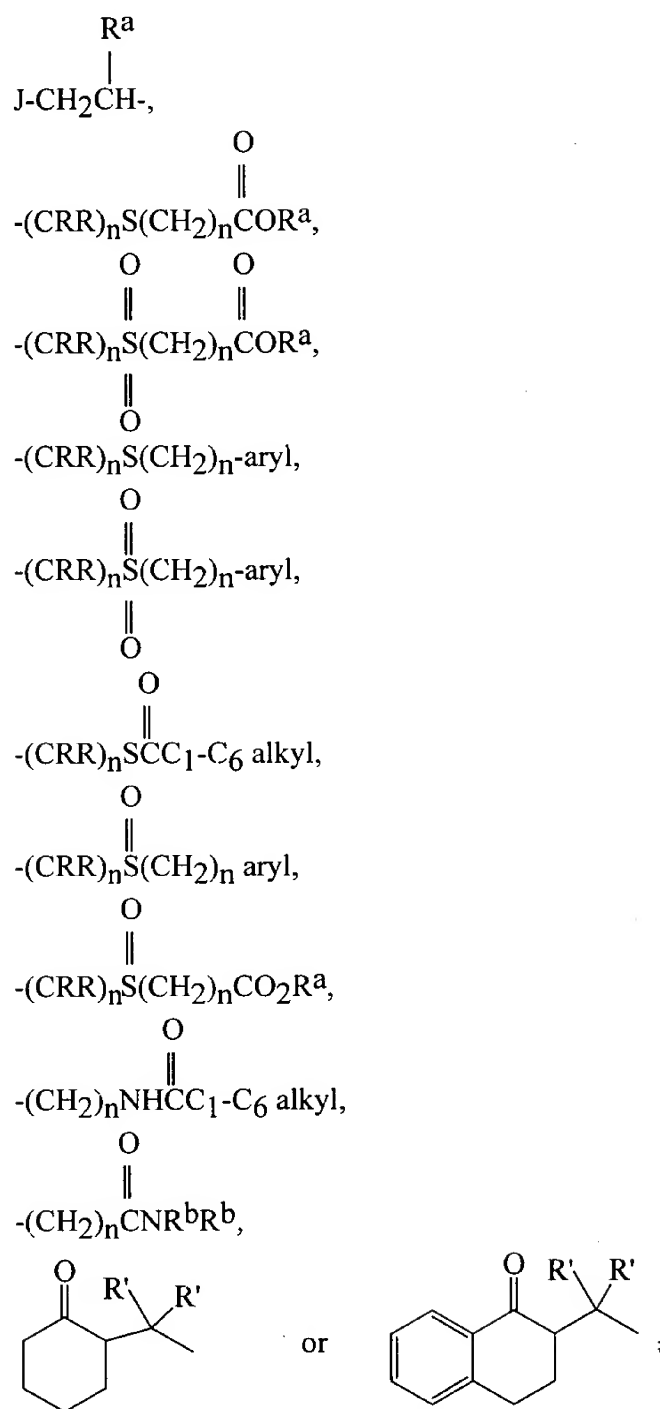
R³ is C₁-C₆ alkyl,
 aryl,
 $-(CHR)_n$ -aryl,
 $-(CHR)_n$ -substituted aryl,

$\begin{array}{c} O \\ || \\ -(CRR)_n COR^a, \\ -(CRR)_n O(CH_2)_n \text{ aryl,} \\ \text{cycloalkyl,} \\ \text{substituted cycloalkyl,} \end{array}$

$\begin{array}{c} O \\ || \\ -(CRR)_n CNR^a R^a, \end{array}$

$\begin{array}{c} O \\ || \\ -(CRR)_n S-(CH_2)_n \text{ aryl,} \end{array}$

$\begin{array}{c} O \\ || \\ O \\ || \\ -(CRR)_n SC_1-C_6 \text{ alkyl,} \\ O \end{array}$



each R' is independently C₁-C₆ alkyl,
 C₁-C₆ alkylaryl,
 aryl, or
 hydrogen;

each J is independently

~~-NH-SO₂-(C₁-C₆-alkyl),~~

-CO₂R^b,

-CONR^bR^b,

-SO₂NR^bR^b, or

-SO₂R^b;

each R^b is independently hydrogen, C₁-C₆ alkyl, aryl, substituted aryl, arylalkyl, or substituted arylalkyl;

R⁴ is hydrogen,

C₁-C₆ alkyl,

$\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_3\text{OC}- \end{array}$,

-phenyl, or

$\begin{array}{c} \text{O} \\ \parallel \\ \text{C}_1\text{-C}_6 \text{ alkyl C}- \end{array}$;

R⁵ is C₁-C₆ alkyl-CO-,

-(CH₂)_naryl,

$\begin{array}{c} \text{O} \\ \parallel \\ \text{C}_1\text{-C}_6\text{-alkylOC}- \end{array}$,

C₁-C₆-alkyl-X-(CH₂)_nCO,

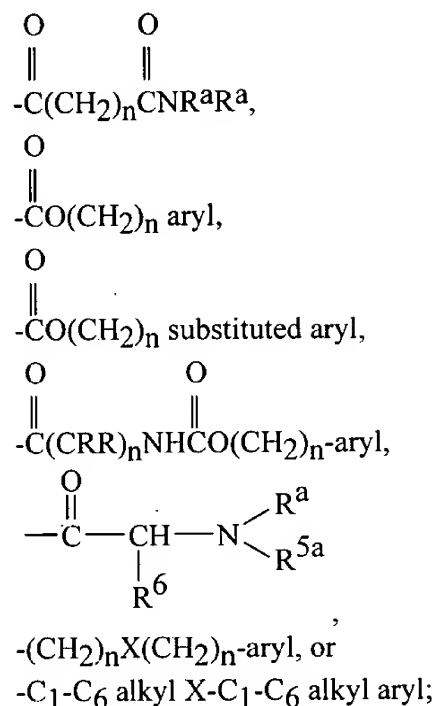
$\begin{array}{c} \text{O} \\ \parallel \\ \text{C}_1\text{-C}_6\text{-alkyl-X-(CH}_2\text{)}_n\text{OC}- \end{array}$,

$\begin{array}{c} \text{O} \\ \parallel \\ \text{-C(CRR)}_n\text{aryl,} \end{array}$

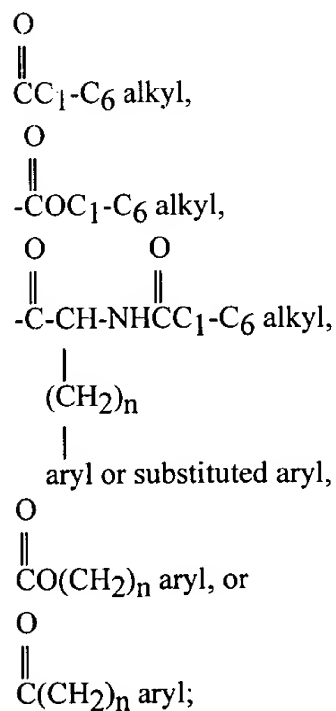
$\begin{array}{c} \text{O} \\ \parallel \\ \text{-CNR}^a\text{R}^a, \end{array}$

$\begin{array}{c} \text{O} \\ \parallel \\ \text{-SC}_1\text{-C}_6 \text{ alkyl,} \end{array}$

$\begin{array}{c} \text{O} \\ \parallel \\ \text{O} \end{array}$



R^{5a} is



R⁶ is hydrogen,

C₁-C₆ alkyl, -(CH₂)_n aryl, -(CH₂)_nCO₂R^a, or hydroxyl substituted C₁-C₆ alkyl;

~~R⁷ is hydrogen, S (C₁-C₆-alkyl), or SO₂-(C₁-C₆-alkyl);~~

each n is independently 0 to 3, and the pharmaceutically acceptable, salts, ~~esters, amides, and prodrugs~~ thereof;

excluding the following compounds:

N-(3-Phenylpropionyl)-L-valine-L-alanine-L-aspartic acid 2,6-dihydroxy-benzoyloxymethyl ketone;

N-(3-Phenylpropionyl)-L-valine-L-alanine-L-aspartic acid 2,6-dimethyl-benzoyloxymethyl ketone;

N-Benzyloxycarbonyl-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;
N-Benzyloxycarbonyl-L-aspartic acid 2,6-ditrifluoromethyl benzoyloxymethyl ketone;

~~N-Benzyloxycarbonyl-L-aspartic acid 2,6-dichloro-3-(2-N-morpholinylethoxy)benzoyloxymethyl ketone;~~

N-Benzyloxycarbonyl-L-aspartic acid 2,6-dimethoxybenzoyloxy methyl ketone;
N-Benzyloxycarbonyl-L-aspartic acid 2,-dichloro-3-(benzyloxy)benzoyloxymethyl ketone;

N-Benzyloxycarbonyl-L-aspartic acid 2-acetamido-6-chlorobenzoyloxymethyl ketone;
N-Benzyloxycarbonyl-L-aspartic acid 2,6-difluorobenzoyloxymethyl ketone;

N-Benzyloxycarbonyl-L-aspartic acid 3-(N-butylsulfonamido)-2,6-dichlorobenzoyloxymethyl ketone;

N-Benzyloxycarbonyl-L-aspartic acid 2,6-dichloro-3-sulfonamido benzoyloxymethyl ketone;

N-Benzyloxycarbonyl-L-aspartic acid 3-(N-benzylsulfonamido)-2,6-dichlorobenzoyloxymethyl ketone;

N-Benzyloxycarbonyl-L-aspartic acid 3-(N-(2-aminoacetamidoyl)-sulfonamido)-2,6-dichlorobenzoyloxymethyl ketone;

~~N-Benzyloxycarbonyl-L-aspartic acid 2,6-dichloro-3-(N-morpholinylsulfonamido)benzoyloxymethyl ketone;~~

N-Methoxycarbonyl-L-alanine-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;

~~N-(2-thienyl)carbonyl-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;~~

N-Methoxycarbonyl glycine-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;
N-Methoxycarbonyl-L-phenylalanine-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;

N-Methoxycarbonyl-L-valine-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;

~~N-Methoxycarbonyl-L-histidine-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;~~

N-Benzyloxycarbonyl-L-valine-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;

N-Benzyloxycarbonyl-L-alanine-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;

N-Benzyloxycarbonyl-L-valine-L-alanine-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;

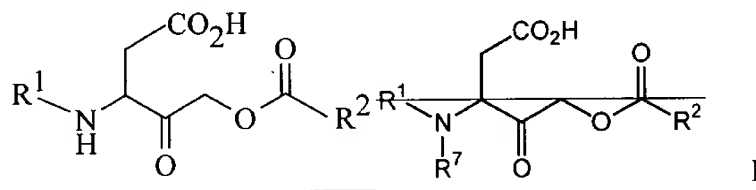
~~N-(2-Furonyl)carbonyl-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;~~

~~N-(2-Furonyl)carbonyl-L-aspartic acid 2,6-dichloro-3-(N-morpholinylsulfonamido)benzoyloxymethyl ketone;~~

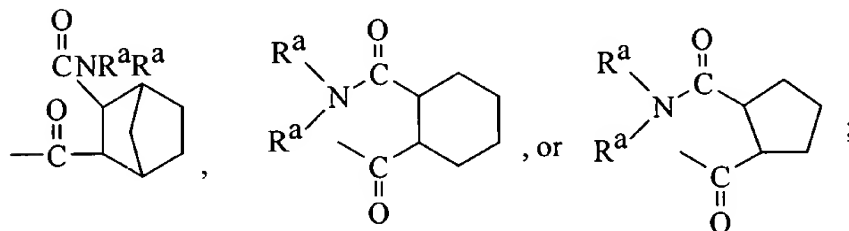
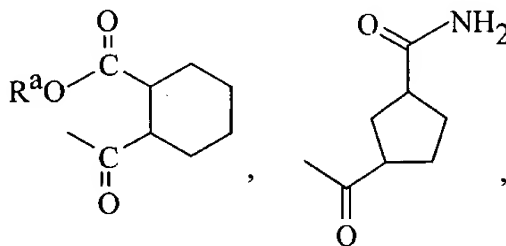
N-(3-Phenylpropionyl)-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;
N-Methoxycarbonyl-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;
N-(4-N,N-dimethylaminomethyl)benzoyl-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;
N-Benzoyloxycarbonyl-D-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;
~~N-Methoxy-L-histidine-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;~~
N-Methoxy-glycine-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;
N-Methoxy-L-alanine-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;
N-Methoxy-L-valine-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;
N-Benzoyloxy-L-valine-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;
N-Benzoyloxy-D-alanine-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;
N-Benzoyloxy-L-alanine-L-alanine-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;
N-Benzoyloxy-L-valine-L-alanine-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;
N-Benzoyloxy-D-alanine-L-alanine-L-aspartic acid 2,6-dichlorobenzoyloxymethyl ketone;
N-(N-phenylpropionyl-valinyl-alaninyl)-3-amino-4-oxo-5-(2,6-bistrifluoromethylbenzoyloxy) pentanoic acid;
N-(N-phenylpropionyl-valinyl-alaninyl)-3-amino-4-oxo-5-benzoyloxy pentanoic acid;
N-(N-Acetyl-tyrosinyl-valinyl-alaninyl)-3-amino-4-oxo-5-(pentafluorobenzoyloxy) pentanoic acid;
3-Phenylpropionyl-L-valine-L-alanine-aspartic acid 2-phenylethylcarbonyloxymethyl ketone;
Adamantane-1-carboxylic acid 3-[2-(2-benzoyloxycarbonylamino-3-methylbutyrylamino)-propionylamino]-4-carboxy-2-oxo-butyl ester;
~~Acridine 9-carboxylic acid 3-[2-(2-benzoyloxycarbonylamino-3-methylbutyrylamino)-propionylamino]-4-carboxy-2-oxo-butyl ester;~~
~~1H-Indole 3-carboxylic acid 3-[2-(2-benzoyloxycarbonylamino-3-methylbutyrylamino)-propionylamino]-4-carboxy-2-oxo-butyl ester;~~
~~2-Methylimidazo[1,2-a]pyridine 3-carboxylic acid 3-[2-(2-benzoyloxycarbonylamino-3-methylbutyrylamino)-propionylamino]-4-carboxy-2-oxo-butyl ester;~~
~~2-Methoxy 3-methyl quinoline 4-carboxylic acid 3-[2-(2-benzoyloxycarbonylamino-3-methylbutyrylamino)-propionylamino]-4-carboxy-2-oxo-butyl ester;~~
~~1,3-Dimethyl 1H-indole 2-carboxylic acid 3-[2-(2-benzoyloxycarbonylamino-3-methylbutyrylamino)-propionylamino]-4-carboxy-2-oxo-butyl ester;~~
~~9H-Xanthene 9-carboxylic acid 3-[2-(2-benzoyloxycarbonylamino-3-methylbutyrylamino)-propionylamino]-4-carboxy-2-oxo-butyl ester;~~
3-[2-(2-Benzoyloxycarbonylamino-3-methylbutyrylamino)-propionylamino]-5-diphenylacetoxy-4-oxo-pentanoic acid;
2,6-Dichloro-benzoic acid 3-(5-benzoyloxycarbonylamino-naphthalene-1-sulfonylamino)-4-carboxy-2-oxo-butyl ester;
~~2,6-Dichloro-benzoic acid 3-[[2-(1-benzoyloxycarbonylamino-2-methyl-propyl)-thiazole-4-carbonyl]-amino]-4-carboxy-2-oxo-butyl ester;~~
2,6-Dichloro-benzoic acid 3-[2-(3-benzoyloxycarbonylamino-phenyl)-propionylamino]-4-carboxy-2-oxo-butyl ester;
~~2,6-Dichloro-benzoic acid 3-[(5-benzoyloxycarbonylamino-1H-indole-3-carbonyl)-amino]-4-carboxy-2-oxo-butyl ester;~~

2,6-Dichloro-benzoic acid 3-[2-(6-benzyloxycarbonyloxy-naphthalen-2-yl)-propionylamino]-4-carboxy-2-oxo-butyl ester;
 2,6-Dichloro-benzoic acid 3-(5-benzyloxycarbonylamino-naphthalene-1-sulfonylamino)-4-carboxy-2-oxo-butyl ester;
 2,6-Dichloro-benzoic acid 3-[(5-benzyloxycarbonylamino-naphthalene-1-carbonyl)-amino]-4-carboxy-2-oxo-butyl ester; and
~~2,6-Dichloro-benzoic acid 3-[(6-benzyloxycarbonylamino-5-oxo-octahydro-indolizino-3-carbonyl)-amino]-4-carboxy-2-oxo-butyl ester; and~~
 2,6-Dichloro-benzoic acid 3-[(4-benzyloxycarbonylamino-cyclohexanecarbonyl)-amino]-4-carboxy-2-oxo-butyl ester.

52. (Amended) A compound of the Formula I

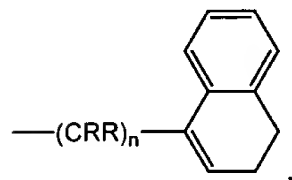
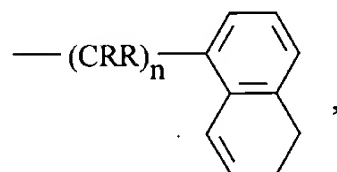
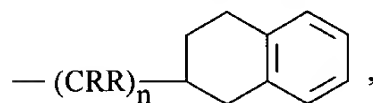
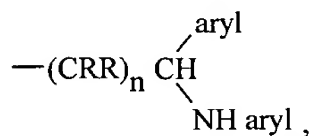
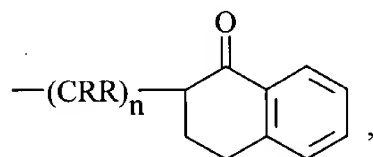
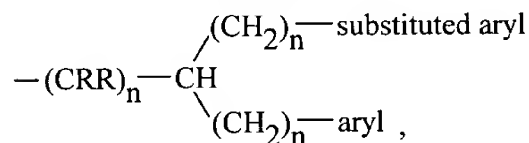
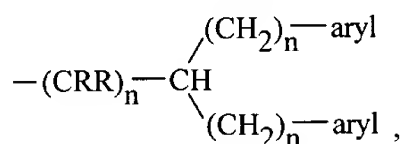


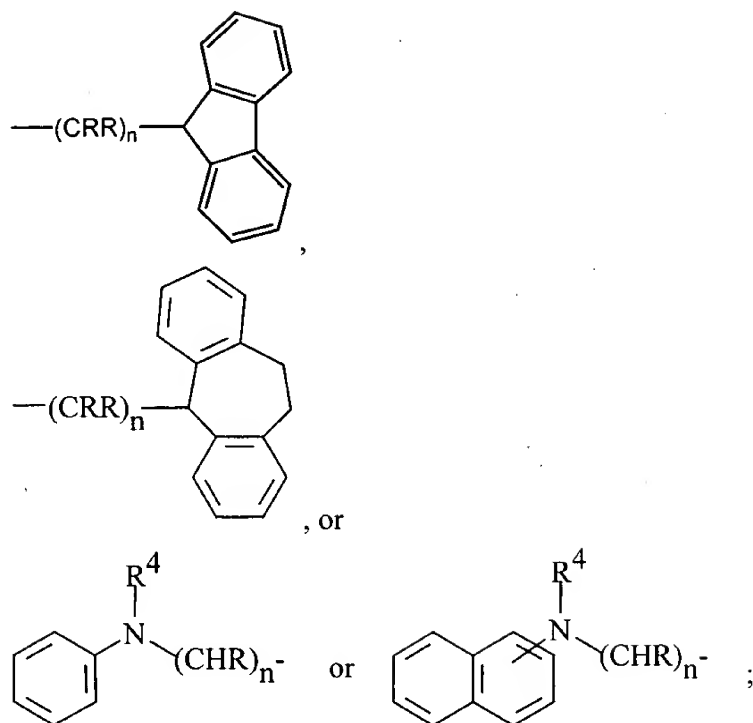
wherein R^1 is $R^3OC(=O)-$,
 R^3CO- ,
 R^3SO_2- ,
 R^a
 $|$
 $R^5NCH(R^6)CO-$,



each R^a is independently hydrogen, C_1 - C_6 alkyl, or $-(CH_2)_n$ aryl;

R^2 is $-(CRR)_n$ -aryl,
 $-(CRR)_n$ -X-aryl,
 $-(CRR)_n$ -(substituted-aryl), provided that the aryl group is not substituted with
 alkoxy, halogen, or trifluoromethyl,
 $-(CRR)_n$ -X-(substituted-aryl),
 $-(CRR)_n$ -aryl-aryl,
 $-(CRR)_n$ -aryl- $(CH_2)_n$ -aryl,
 $-(CRR)_n$ -CH(aryl) $_2$,
 $-(CRR)_n$ -cycloalkyl,
 $-(CRR)_n$ -X-cycloalkyl,





each R is independently hydrogen, C_1 - C_6 alkyl, halogen or hydroxy;

X is O or S;

R^3 is C_1 - C_6 alkyl,

aryl,

$-(CHR)_n$ -aryl,

$-(CHR)_n$ -substituted aryl,

O

||

$-(CRR)_n$ COR^a,

$-(CRR)_n$ O(CH₂)_n-aryl,

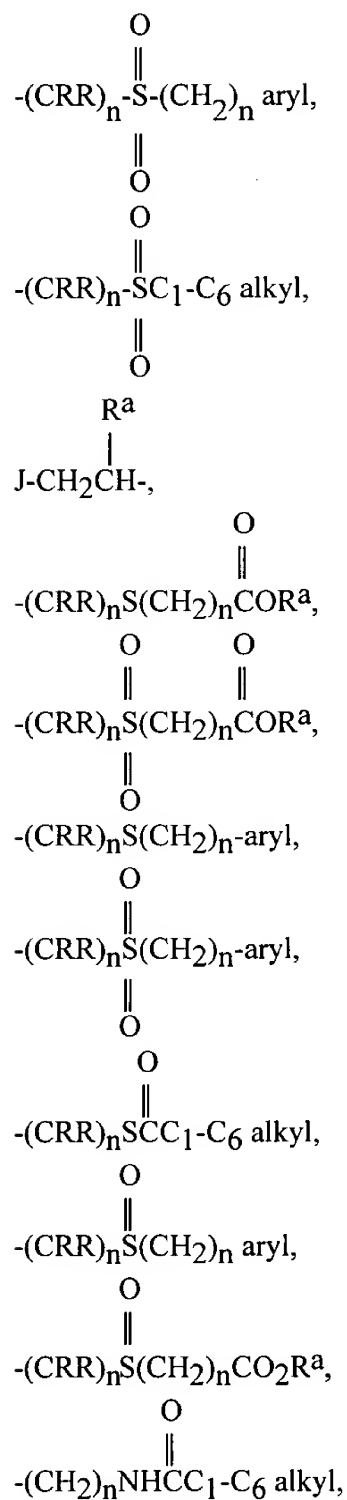
cycloalkyl,

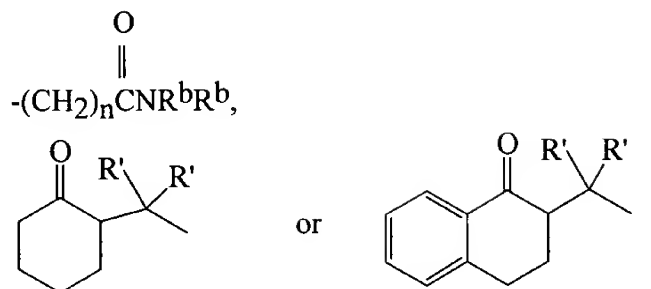
substituted cycloalkyl,

O

||

$-(CRR)_n$ CNR^aR^a,



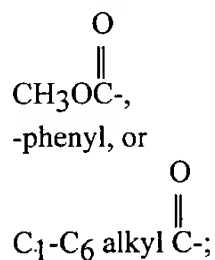


each R' is independently C₁-C₆ alkyl,
 C₁-C₆ alkylaryl,
 aryl, or
 hydrogen;

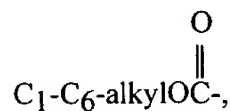
each J is independently
~~NH-SO₂-(C₁-C₆-alkyl),~~
 -CO₂R^b,
 -CONR^bR^b,
 -SO₂NR^bR^b, or
 -SO₂R^b;

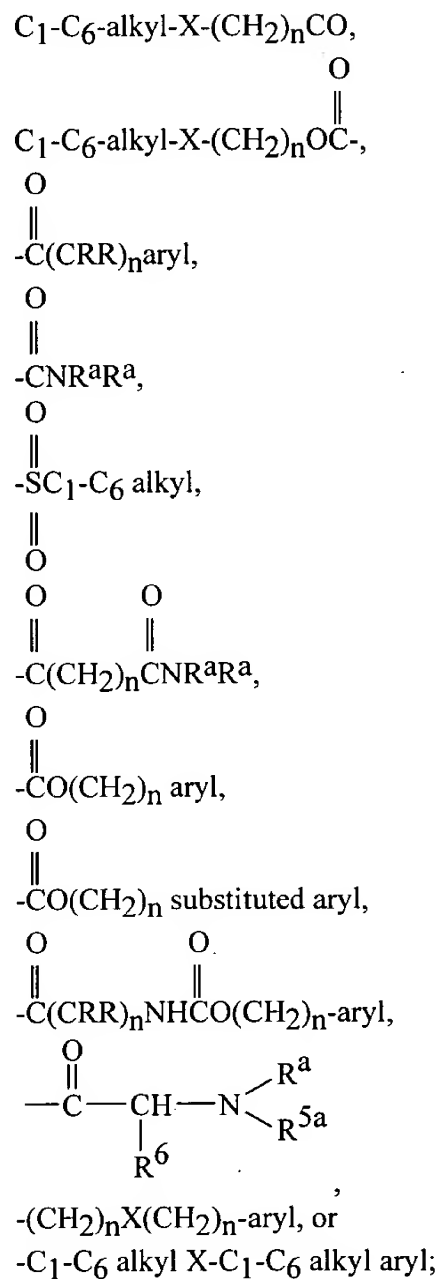
each R^b is independently hydrogen, C₁-C₆ alkyl, aryl, substituted aryl, arylalkyl, or
 substituted arylalkyl;

R⁴ is hydrogen,
 C₁-C₆ alkyl,

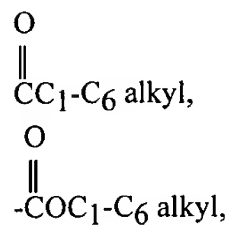


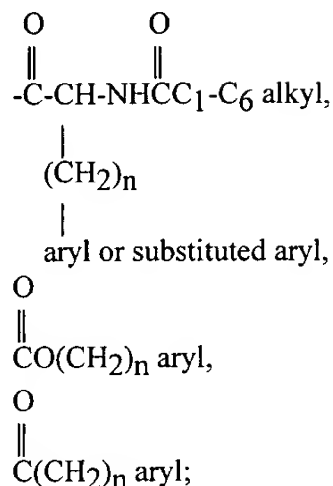
R⁵ is C₁-C₆ alkyl-CO-,
 -(CH₂)_n aryl,





R^{5a} is



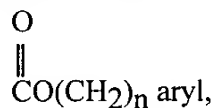


R⁶ is hydrogen, C₁-C₆ alkyl, -(CH₂)_n aryl, -(CH₂)_nCO₂R^a, or hydroxyl substituted C₁-C₆ alkyl;

~~**R⁷ is hydrogen, S (C₁-C₆-alkyl), or SO₂ (C₁-C₆-alkyl);**~~

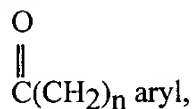
each n is independently 0 to 3,

provided that when R^{5a} is



then n is 0, 2, or 3, and

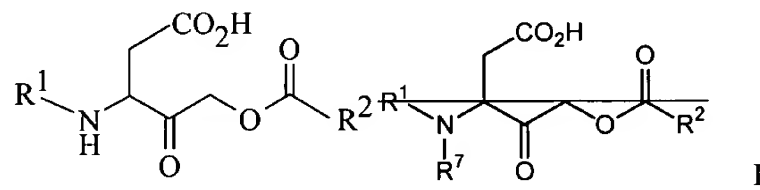
provided that when R^{5a} is



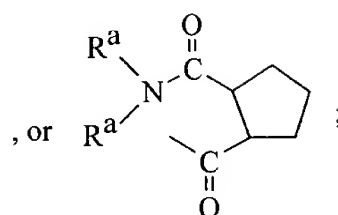
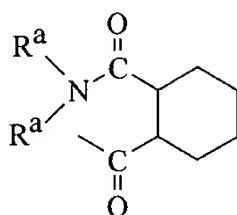
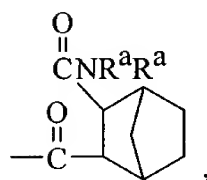
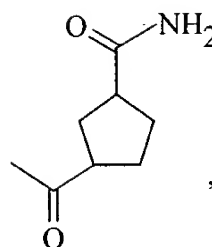
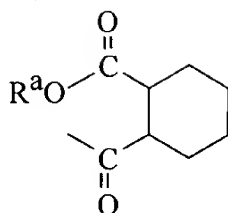
then n is 0, 1, or 3,

and the pharmaceutically acceptable, salts, ~~esters, amides, and prodrugs~~ thereof.

53. (Amended) A compound of the Formula I

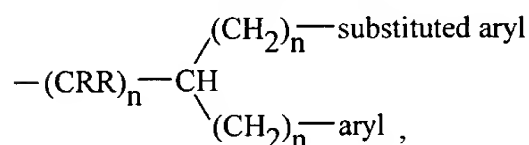
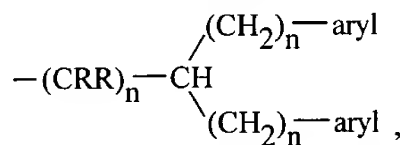


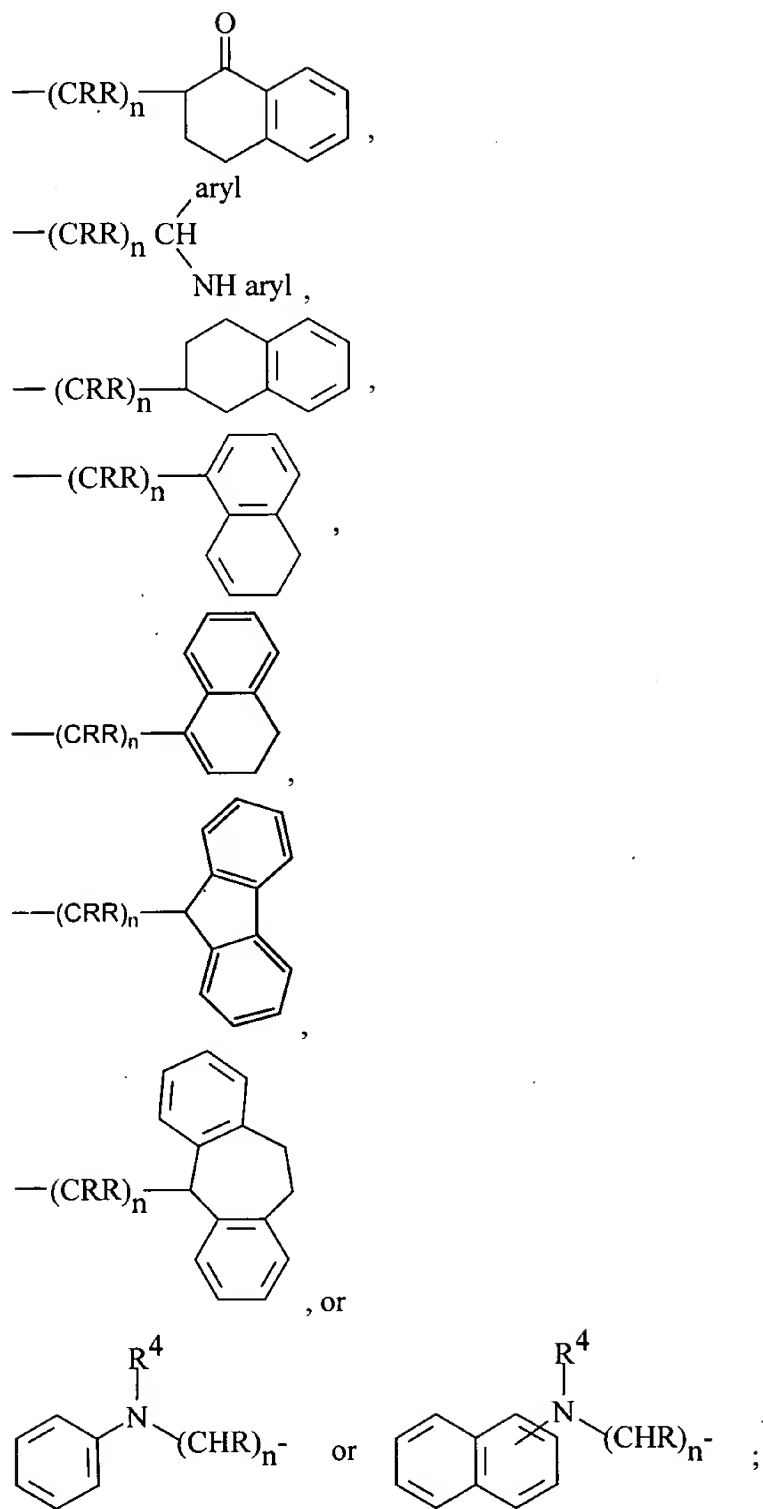
wherein R¹ is $\text{R}^3\text{OC}-$,
 $\text{R}^3\text{CO}-$,
 R^3SO_2- ,
 R^a
 $|$
 $\text{R}^5\text{NCHR}^6\text{CO}-$,



each R^a is independently hydrogen, C₁-C₆ alkyl, or $-(\text{CH}_2)_n$ aryl;

R² is $-(\text{CRR})_n$ -aryl,
 $-(\text{CRR})_n$ -X-aryl,
 $-(\text{CRR})_n$ -X-(substituted-aryl),
 $-(\text{CRR})_n$ -aryl-aryl,
 $-(\text{CRR})_n$ -aryl- $(\text{CH}_2)_n$ -aryl,
 $-(\text{CRR})_n$ -CH(aryl)₂,
 $-(\text{CRR})_n$ -cycloalkyl,
 $-(\text{CRR})_n$ -X-cycloalkyl,





each R is independently hydrogen, C₁-C₆ alkyl, halogen or hydroxy;

X is O or S;

R^3 is C_1 - C_6 alkyl,
 aryl,
 $-(CHR)_n$ -aryl,
 $-(CHR)_n$ -substituted aryl,

$\begin{array}{c} O \\ || \\ -(CRR)_nCOR^a, \\ -(CRR)_nO(CH_2)_n\text{-aryl,} \\ \text{cycloalkyl,} \\ \text{substituted cycloalkyl,} \end{array}$

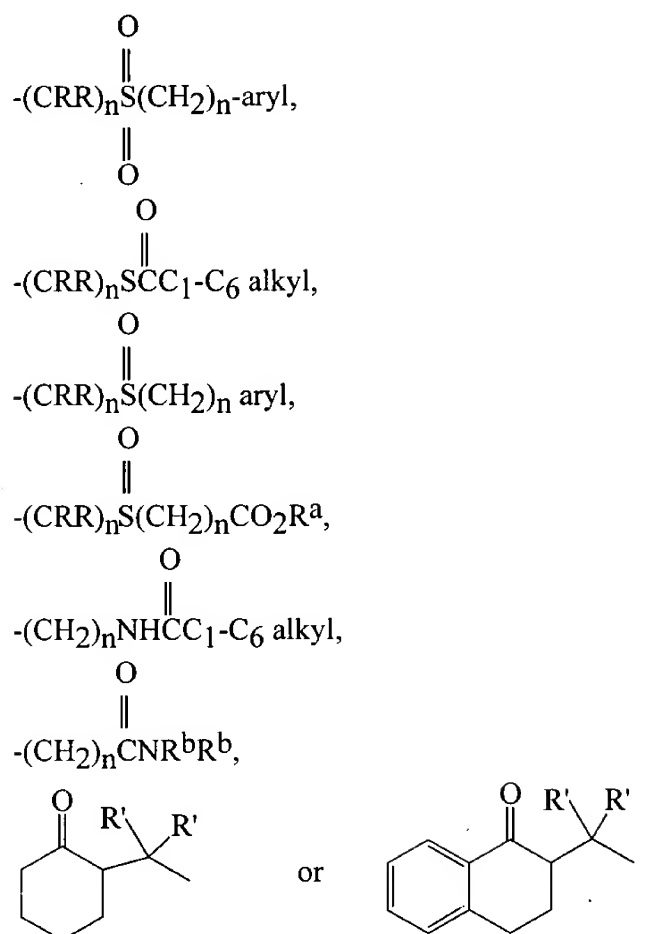
$\begin{array}{c} O \\ || \\ -(CRR)_nCNR^aR^a, \\ \begin{array}{c} O \\ || \\ -(CRR)_n-S-(CH_2)_n\text{ aryl,} \end{array} \end{array}$

$\begin{array}{c} O \\ || \\ O \\ || \\ -(CRR)_n-SC_1-C_6\text{ alkyl,} \\ O \end{array}$

$\begin{array}{c} R^a \\ | \\ J-CH_2CH-, \end{array}$

$\begin{array}{c} O \\ || \\ -(CRR)_nS(CH_2)_nCOR^a, \\ \begin{array}{cc} O & O \\ || & || \\ -(CRR)_nS(CH_2)_nCOR^a, \end{array} \end{array}$

$\begin{array}{c} O \\ || \\ -(CRR)_nS(CH_2)_n\text{-aryl,} \end{array}$



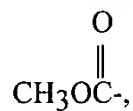
each R' is independently C₁-C₆ alkyl,
 C₁-C₆ alkylaryl,
 aryl, or
 hydrogen;

each J is independently
~~NH-SO₂-(C₁-C₆-alkyl),~~
 -CO₂R^b,
 -CONR^bR^b,
 -SO₂NR^bR^b, or
 -SO₂R^b;

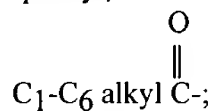
each R^b is independently hydrogen, C₁-C₆ alkyl, aryl, substituted aryl, arylalkyl, or
 substituted arylalkyl;

R⁴ is hydrogen,

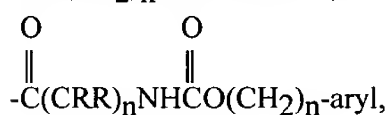
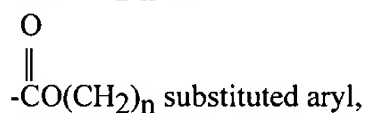
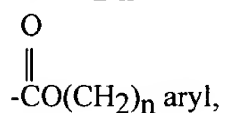
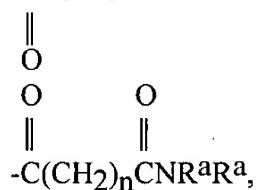
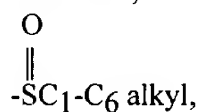
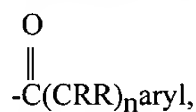
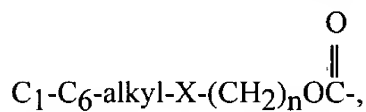
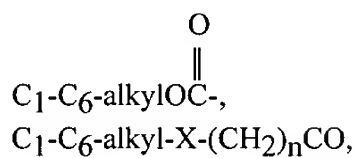
C₁-C₆ alkyl,

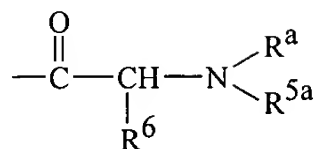


-phenyl, or



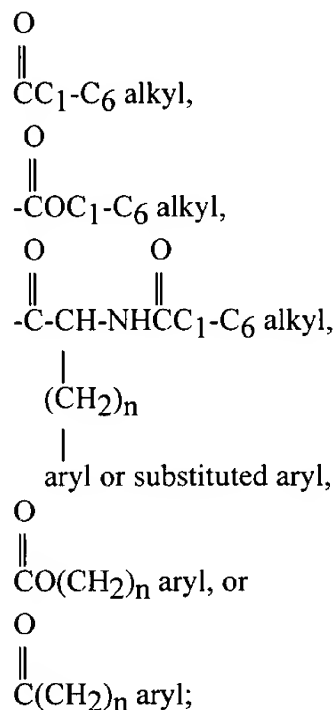
R⁵ is C₁-C₆ alkyl-CO-,
 -(CH₂)_n aryl,





-(CH₂)_nX(CH₂)_n-aryl, or
 -C₁-C₆ alkyl X-C₁-C₆ alkyl aryl;

R^{5a} is

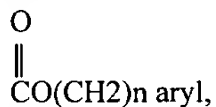


R⁶ is hydrogen, C₁-C₆ alkyl, -(CH₂)_n aryl, -(CH₂)_nCO₂R^a, or hydroxyl substituted C₁-C₆ alkyl;

~~R⁷ is hydrogen, S (C₁-C₆ alkyl), or SO₂-(C₁-C₆ alkyl);~~

each n is independently 0 to 3,

provided that when R^{5a} is

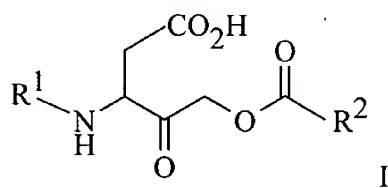


then n is 0, 2, or 3, and

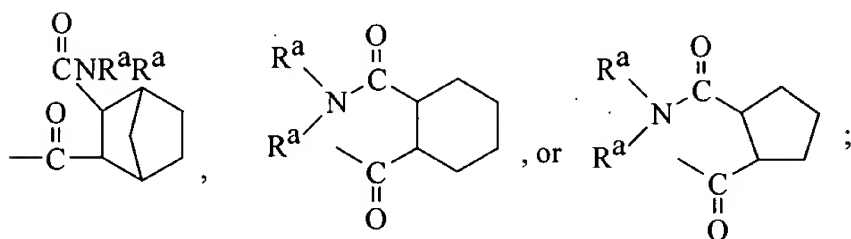
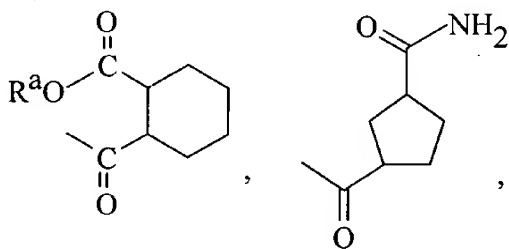
provided that when R^{5a} is

$$\begin{array}{c} \text{O} \\ \parallel \\ \text{C}(\text{CH}_2)_n \text{ aryl,} \end{array}$$
 then n is 0, 1, or 3,
 and the pharmaceutically acceptable, salts, ~~esters, amides, and prodrugs~~ thereof.

54. (Amended) A compound of the Formula I



wherein R¹ is $\begin{array}{c} \text{O} \\ \parallel \\ \text{R}^3\text{OC-} \end{array}$,
 $\text{R}^3\text{CO-}$,
 $\text{R}^3\text{SO}_2\text{-}$,
 $\begin{array}{c} \text{R}^a \\ | \\ \text{R}^5\text{NCHR}^6\text{CO-} \end{array}$,



each R^a is independently hydrogen, C₁-C₆ alkyl, or -(CH₂)_n aryl;

R² is -(CRR)_n-aryl,
 -(CRR)_n-X-aryl,


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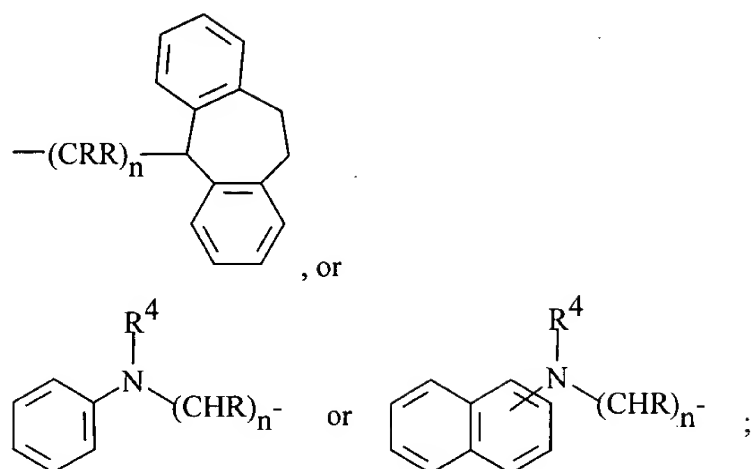
-(CRR)_n-aryl-aryl,

$$-(\text{CRR})_n-\text{CH}(\text{aryl})_2,$$

-(CRR)_n-cycloalkyl,

-(CRR)_n-X-cycloalkyl,

$$-(\text{CRR})_n-\text{CH} \begin{array}{l} \diagup (\text{CH}_2)_n-\text{aryl} \\ \diagdown (\text{CH}_2)_n-\text{aryl} \end{array}$$
$$-(\text{CRR})_n-\text{CH} \begin{array}{l} \nearrow (\text{CH}_2)_n-\text{substituted aryl} \\ \searrow (\text{CH}_2)_n-\text{aryl} \end{array},$$
*C1CCC2=C(C1)C(=O)C3=CC=CC=C23
$$-(\text{CRR})_n \text{CH} \begin{array}{l} \nearrow \text{aryl} \\ \searrow \text{NH aryl} \end{array},$$
$$-(\text{CRR})_n-$$

$$-(\text{CRR})_n-\text{C}_{10}\text{H}_7-$$



each R is independently hydrogen, C₁-C₆ alkyl, halogen or hydroxy;

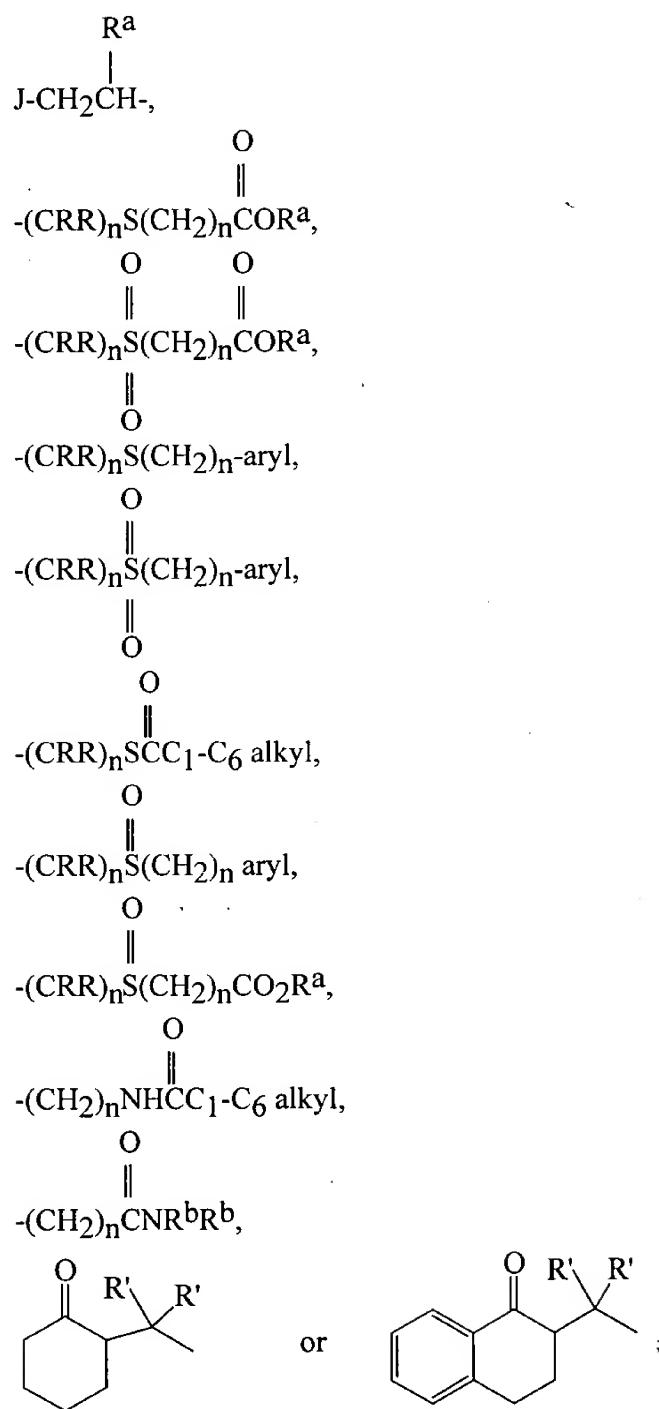
X is O or S;

R³ is C₁-C₆ alkyl,
 aryl,
 -(CHR)_n-aryl,
 -(CHR)_n-substituted aryl,

O
 ||
 -(CRR)_nCOR^a,
 -(CRR)_nO(CH₂)_n-aryl,
 cycloalkyl,
 substituted cycloalkyl,

O
 ||
 -(CRR)_nCNR^aR^a,
 O
 ||
 -(CRR)_n-S-(CH₂)_n aryl,

O
 O
 ||
 -(CRR)_n-SC₁-C₆ alkyl,
 O



each R' is independently C₁-C₆ alkyl,
 C₁-C₆ alkylaryl,
 aryl, or
 hydrogen;

each J is independently

~~-NH-SO₂-(C₁-C₆-alkyl),~~
 -CO₂R^b,
 -CONR^bR^b,
 -SO₂NR^bR^b, or
 -SO₂R^b;

each R^b is independently hydrogen, C₁-C₆ alkyl, aryl, substituted aryl, arylalkyl, or substituted arylalkyl;

R⁴ is hydrogen,

C₁-C₆ alkyl,

$\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_3\text{OC}- \end{array}$,

-phenyl, or

$\begin{array}{c} \text{O} \\ \parallel \\ \text{C}_1\text{-C}_6 \text{ alkyl C}- \end{array}$;

R⁵ is C₁-C₆ alkyl-CO-,

-(CH₂)_n aryl,

$\begin{array}{c} \text{O} \\ \parallel \\ \text{C}_1\text{-C}_6\text{-alkylOC}- \end{array}$,

C₁-C₆-alkyl-X-(CH₂)_nCO,

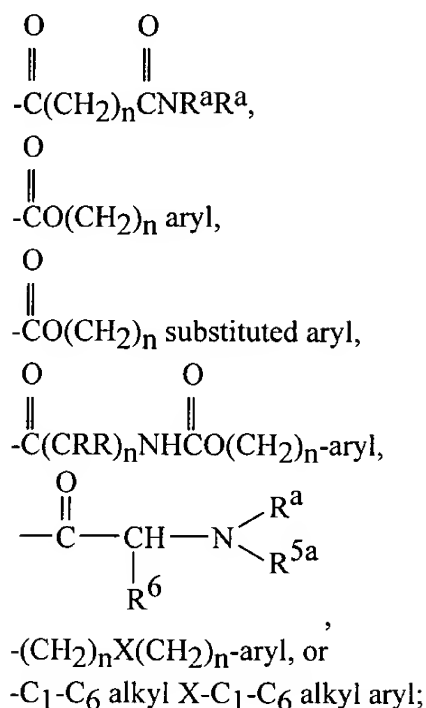
$\begin{array}{c} \text{O} \\ \parallel \\ \text{C}_1\text{-C}_6\text{-alkyl-X-(CH}_2\text{)}_n\text{OC}- \end{array}$,

$\begin{array}{c} \text{O} \\ \parallel \\ \text{-C(CRR)}_n\text{aryl;} \end{array}$

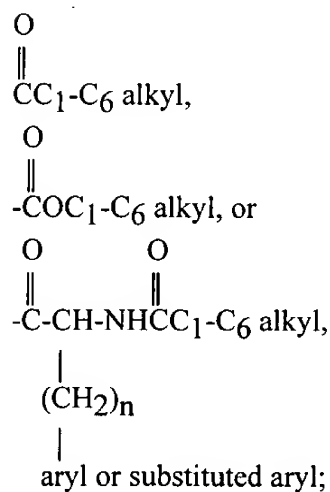
$\begin{array}{c} \text{O} \\ \parallel \\ \text{-CNR}^a\text{R}^a, \end{array}$

$\begin{array}{c} \text{O} \\ \parallel \\ \text{-SC}_1\text{-C}_6 \text{ alkyl,} \end{array}$

$\begin{array}{c} \text{O} \\ \parallel \\ \text{O} \end{array}$



R^{5a} is



R^6 is hydrogen, $\text{C}_1\text{-C}_6$ alkyl, $-(\text{CH}_2)_n$ aryl, $-(\text{CH}_2)_n \text{CO}_2 \text{R}^a$, or hydroxyl substituted $\text{C}_1\text{-C}_6$ alkyl;

~~R^7 is hydrogen, $\text{-S-}(\text{C}_1\text{-C}_6 \text{ alkyl})$, or $\text{-SO}_2\text{-(C}_1\text{-C}_6 \text{ alkyl)}$;~~

each n is independently 0 to 3, and the pharmaceutically acceptable, salts, ~~esters, amides,~~
~~and prodrugs~~ thereof.